David E. De Lorenzi, Esq.
Sheila F. McShane, Esq.
GIBBONS P.C.
One Gateway Center
Newark, New Jersey 07102-5310
Telephone No.: (973) 596-4500
Facsimile No.: (973) 596-0545

Of Counsel:
Bartholomew Verdirame, Esq.
Michael P. Dougherty, Esq.
Tony V. Pezzano, Esq.
Kent Stevens, Esq.
Jeffrey Z. Y. Liao, Esq.
Vinny Lee, Esq.
Christopher Dove, Esq.
CADWALADER, WICKERSHAM & TAFT LLP
1 World Financial Center
New York, New York 10281
Telephone No.: (212) 504-6000
Facsimile No.: (212) 504-6666

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ROCHE PALO ALTO LLC, **Plaintiff,** **-against-** **RANBAXY LABORATORIES LIMITED AND RANBAXY, INC.,** **Defendants.**	**Civil Action No. 06-2003** **Judge Freda L. Wolfson** **Magistrate Judge Tonianne J. Bongiovanni** **PLAINTIFF ROCHE PALO ALTO LLC'S PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW**

This matter having come before the Court for trial during the period December 1 through December 22, 2008 in Trenton in Courtroom 6E before The Honorable Freda L. Wolfson. Pursuant to the Court's Post Trial Briefing Schedule as ordered on January 7, 2009, Plaintiff Roche Palo Alto LLC submits the following Proposed Findings Of Fact And Conclusions Of Law.

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PART I: PROPOSED FINDINGS OF FACT

I. BACKGROUND

A. Nature Of The Action

1. This is a patent case brought by Roche Palo Alto LLC ("Roche") against Ranbaxy Laboratories Ltd. and Ranbaxy, Inc. (collectively, "Ranbaxy") under 35 U.S.C. §271(e)(2) for infringement of Roche's U.S. Patent No. 6,083,953 ("the '953 patent"). This action was precipitated by Ranbaxy's filing of an Abbreviated New Drug Application ("ANDA") for approval to market a generic version of Roche's antiviral drug Valcyte® prior to the expiration of Roche's '953 patent.

B. CMV, Valcyte, And The '953 Patent

2. Cytomegalovirus ("CMV") is present in 50 to 70% of the adult population and generally produces no symptoms. However, CMV can cause serious problems in persons with depressed immune systems, such as AIDS patients and individuals who are taking immunosuppressive medication to prevent the rejection of a transplanted organ. Drew Tr. I 84:21-85:23; Snydman Stip. ¶5. In AIDS patients, its most common manifestation is "CMV retinitis," which can result in blindness. Drew Tr. I 85:24-86:2. In organ transplant recipients, CMV can cause rejection of the transplanted organ. Snydman Stip. ¶6. CMV also increases the cost of medical care in the first year after the transplant by 40 to 80%. Snydman Stip. ¶7.

3. Valcyte is an orally administered antiviral medication that is approved by the FDA for the treatment of CMV retinitis in AIDS patients and for the prevention of CMV disease in organ transplant recipients. Lesser Tr. I 56:3-22; PTX-653 at 8. It is considered the "gold standard," the "drug of choice," the "treatment of choice," and the "standard of care" for the prevention and treatment of CMV disease. Tate Tr. VIII 159:5-11; Drew Tr. I 86:3-6; Snydman Stip.¶¶8, 22.

The active ingredient in Valcyte is valganciclovir hydrochloride in crystalline form. Lesser Tr. I 55:1-12; PTX-653 at lns. 11, 19.

4. The '953 patent (PTX-1) contains six claims, of which Claim 1 is the only independent claim. It is undisputed that the compound recited in Claim 1 is valganciclovir hydrochloride in crystalline form. Mitscher Tr. IX 85:11-13. Claim 2 is directed to a pharmaceutical composition comprising that compound. And Claims 3-6 are directed to methods of treating viral infections by administering that compound.

C. Ranbaxy's ANDA No. 78-078

5. On December 22, 2005, Ranbaxy filed an ANDA seeking approval to market generic 450 mg valganciclovir hydrochloride tablets for the same indications as Valcyte. Henck Tr. II 120:12-121:11; PTX-286 at RVHRX0000104. In its subsequent notice to Roche pursuant to 21 U.S.C. §355(j)(2)(B)(iv), Ranbaxy set forth only one defense: that its product would not infringe the '953 patent because the patent requires the claimed valganciclovir hydrochloride to be "in crystalline form," whereas Ranbaxy's valganciclovir hydrochloride is purportedly in amorphous form. PTX-287 at 2. Ranbaxy did not assert that the patent is invalid or unenforceable on any ground.

D. The Crystalline Form Of Matter And Its Detection By X-Ray Diffraction

6. A crystalline material is characterized by molecules organized into a repeating pattern in three dimensions. By contrast, an amorphous material has molecules that are distributed randomly. Henck Tr. II 80:2-13; X 175:10-177:1, 180:21-181:2; PTX-772 at 1 ("Solids may be crystalline or amorphous, and the crystalline state differs from the amorphous state in the regular arrangement of the constituent molecules, atoms or ions into some fixed and rigid pattern known as a lattice."). A material can be either crystalline or amorphous; there is no intermediate state in between these two forms. Henck Tr. II 98:22-24.

7. An amorphous material has greater free energy than a crystalline material due to the random distribution of its molecules and is thermodynamically inclined to convert to crystalline form. Henck Tr. II 80:2-23. Increases in temperature, and exposure to water or humidity can promote the conversion of an amorphous material to crystalline form. Henck Tr. II 80:24-82:2.

8. For over 80 years, the standard test for detecting a compound in crystalline form has been powder X-ray diffraction, or "XRD." Henck Tr. II 83:1-6. Ranbaxy's experts called XRD "the primary method of choice" among persons of skill in the art and the "best technique" for determining whether a material is in crystalline form. Rogers Tr. VI 162:22-164:4; Cockcroft Tr. VII 42:6-44:2. Ranbaxy itself relied on XRD as the sole basis for the contention in its Paragraph IV notice that its valganciclovir hydrochloride is not "in crystalline form." Henck Tr. II 105:4-106:8; PTX-287 at 3.

9. When a crystalline material is subjected to XRD, the X-rays are diffracted at specific angles ("degrees 2θ" or "°2θ"), resulting in a pattern of one or more "peaks." Henck Tr. II 83:13-84:14. An amorphous material does not produce peaks when subjected to XRD, but produces a smooth "halo" pattern. Henck Tr. II 84:8-14, 93:15-94:9; PTX-747; DX-183 at 7.

II. CONSTRUCTION OF THE '953 PATENT CLAIMS

A. To A Person Of Skill In The Art, "In Crystalline Form" Means A Regularly Repeating Three Dimensional Pattern Of Molecules

10. Claim 1 of the '953 patent has three limitations: (1) the compound valganciclovir; (2) as the hydrochloride salt; (3) in crystalline form. Gokel Tr. VII 105:16-106:8. The only limitation in dispute is the requirement that the compound be "in crystalline form."

11. A person of skill in the art with respect to the '953 patent would be a medicinal chemist or drug formulator with an advanced academic degree and some industry experience or a lesser academic degree and a longer period of experience. Mitscher Tr. IX 59:16-24. As of the '953

patent's July 28, 1994, filing date, a person of skill in the art would have understood that the term "in crystalline form" means that the molecules in a given material are arranged in a regularly repeating three-dimensional pattern. FF 6.

B. To A Person Of Skill In The Art, Claim 1 Covers Crystalline Valganciclovir Hydrochloride Regardless Of How Or When The Compound Comes Into Existence Or The Quantity Present And Is Not Limited By Any XRD Fingerprint

12. Roche's expert Dr. Henck reviewed the claims and entire specification of the '953 patent along with relevant portions of the prosecution history in order to reach an expert opinion regarding the meaning of the claims. Henck Tr. II 100:15-101:19; PTX-1; DX-5; DX-8; DX-10.

13. Claim 1 is a compound claim, not a manufacturing claim, and reads on valganciclovir hydrochloride in crystalline form regardless of how it is produced. Thus, there is no requirement in Claim 1 that valganciclovir hydrochloride must be manufactured in crystalline form. Henck Tr. II 108:11-21; *see also* Henck Tr. II 101:20-102:2; 104:23-105:3; Rogers Tr. VI 183:19-184:18; PTX-1.

14. The '953 patent specification confirms that Claim 1 contains no manufacturing limitations. It describes the valganciclovir compound as one aspect of the invention and distinguishes it from methods of making the compound. *Compare* PTX-1 ('953:col. 5, lns. 66-6:19 (describing compound as "first aspect" of invention) *with* col. 6, lns. 52-61 (describing method of making compound as "fifth aspect" of invention)). During prosecution of the '991 application underlying the '953 patent, the Examiner stated that the claims of the application "are not manufacture claims." DX-8 at 171; Rogers Tr. VI 182:7-183:18.

15. The presence of any amount of crystalline valganciclovir hydrochloride detectable by XRD in a given sample is sufficient to infringe the '953 patent. There is no requirement in the

specification or claims of the '953 that a specific amount of crystalline material be present in order to infringe. Henck Tr. II 108:4-10; PTX-1.

16. There is no language in Claim 1, the specification, or the prosecution history that requires the claimed compound to be made at any particular time. Thus, any crystalline valganciclovir hydrochloride that forms by way of conversion of amorphous valganciclovir hydrochloride after the tablets are manufactured would infringe Claim 1.

17. There is no requirement in the claims or specification of the '953 patent for a specific XRD "fingerprint" pattern for valganciclovir hydrochloride in crystalline form. Henck Tr. II 107:16-108:3; PTX-1.

C. Dependent Claims 2-6

18. The meaning of the terms in Claims 2-6 is discussed in CL 8-9. In claim 4, the reference to "the method of Claim 2" is an obvious typographical error. Claim 4 is referring back to a method claim. Claim 2, however, is not a method claim. Claim 3 is the only method claim that appears prior to Claim 4. Therefore, it is obvious that claim 4 was intended to recite "the method of Claim 3." Henck Tr. III 51:14-16, 52:8-54:14.

III. RANBAXY'S PROPOSED VALGANCICLOVIR HYDROCHLORIDE TABLETS

A. Ranbaxy First Manufactures Its Valganciclovir Hydrochloride API In Crystalline Form Using The Benefits Taught By Roche's '953 Patent

19. Dr. Chandra Khanduri and Mukesh Sharma, Associate Directors of Chemical Research at Ranbaxy, testified that Ranbaxy chose to manufacture its valganciclovir hydrochloride API in crystalline form for "ease of handling and operating" prior to subjecting the crystalline API to a spray-drying process. Khanduri Tr. IV 18:25-19:21, 77:2-18, 85:11-17; Sharma Tr. II 7:2-11 (Video Dep. Tr. 176:21-177:7, 179:6-180:7). Thus, Ranbaxy took full advantage of the teachings of the '953 patent regarding manufacturing its valganciclovir hydrochloride in

crystalline form for the purpose of ease of manufacturing and handling. *See*, *e.g.*, PTX-1 ('953:col. 21, lns. 21-31). In fact, Ranbaxy's PCT application for its valganciclovir hydrochloride cites "three times" to the '953 patent for its teachings regarding manufacturing valganciclovir hydrochloride in crystalline form. Henck Tr. II 124:11-14, 125:4-13; Khanduri Tr. IV 55:18-56:11; PTX-303 at RVHRX0025671.

B. Ranbaxy Manufactures Its API In Crystalline Form Then Subjects It To A Spray-Drying Process In A Crude Attempt To Avoid The '953 Patent

20. Ranbaxy spray dries its valganciclovir hydrochloride in crystalline form in order to purportedly convert it to amorphous form. Henck Tr. II 125:14-25, 126:16-127:13; PTX-329. Dr. Khanduri and Mukesh Sharma both testified that Ranbaxy is aware that Roche's '953 patent claims valganciclovir hydrochloride in crystalline form and that Ranbaxy's valganciclovir hydrochloride tablets should not have any amount of crystallinity because of the '953 patent. Sharma Tr. II 5:18-25, 6:15-7:1 (Video Dep. Tr. 233:21-234:8, 236:6-237:4, 238:21-239:3); Khanduri Tr. IV 73:13-74:16; PTX-380. Nonetheless, Ranbaxy's spray-drying process does not "ensure" its valganciclovir hydrochloride is 100 percent amorphous, but leaves crystalline seeds which promote crystallization. Henck Tr. II 127:14-18.

C. After The Spray-Drying Process, Ranbaxy Allows API Containing Up To 0.5% Crystalline Valganciclovir Hydrochloride To Be Used In Its Tablets

21. Following its Standard Test Procedure for determination of crystallinity in its API batches (PTX-338), Ranbaxy's computer calculates the area under the curve at 3.5° 2θ in the XRD pattern of an API sample and compares it with the area under the curve at 3.5° 2θ of a reference standard having 0.5% crystalline valganciclovir hydrochloride. If the area under the curve at 3.5° 2θ of a sample is less than the area under the curve of the reference standard, the sample is permitted to pass through for tablet manufacturing. Chandrashekar Tr. V 121:11-122:10; DX-802.09; DX-802.10.

22. Ranbaxy acknowledges that its tablets can "theoretically. . . include up to 0.5% crystalline valganciclovir hydrochloride." Chandrashekar Tr. V 121:24-125:18, 128:8-21; DX-382; DX-802.14. Ranbaxy's Standard Test Procedure allows batches of its API to pass for tablet manufacture if the amount of crystalline valganciclovir hydrochloride is below 0.5% of the sample. Henck Tr. II 128:4-129:3; PTX-338 at RVHRX0030933.

23. An internal Ranbaxy email dated August 18, 2005 identifies several batches of API tested by Ranbaxy's Standard Test Procedure, including batch number 1546609, as containing crystalline material below 0.5%: "Complies with WS. Crystalline valganciclovir HCl peak is det[e]cted in all the above mentioned batches but it is below LOD. LOD is 0.5%." Henck Tr. II 129:4-130:6; Chandrashekar Tr. V 141:8-142:1; PTX-334A. API batch 1546609 was used to make Exhibit Batch # 1557337 of tablets that is the subject of Ranbaxy's ANDA 78-078. Chandrashekar Tr. V 142:7-143:4; Henck Tr. II 130:7-20; PTX-387; DX-611; PTX-286 at RVHRX0001457.

D. Roche's Expert Dr. Henck Confirmed That Ranbaxy's Tablets As Manufactured And Shipped For Importation Contain Seeds Of Crystalline Valganciclovir Hydrochloride

24. The laboratory at SSCI of Roche's expert Dr. Henck followed Ranbaxy's Standard Test Procedure (PTX-339) when making sample tablets for his crystalline seed study. Dr. Henck has knowledge of how the samples were prepared because he discussed the study with his technicians, reviewed the notebook pages on which they recorded all the steps for the study, and described the experiments in his expert report. Henck Tr. II 143:17-19, 143:23-145:17; 150:3-154:22; PTX-577.

25. Dr. Henck's laboratory used the same XRD instrument and experimental parameters set forth in Ranbaxy's Standard Test Procedure (PTX-339). Just as in Ranbaxy's test procedures, the XRD angle measurement range was lowered from the usual 2 to 40° 2θ to the analytically

relevant range of 3 to 6° 2θ to focus on the 3.5° 2θ peak. Henck Tr. II 145:18-148:12, 150:3-151:3; PTX-339.

26. A total of six samples were prepared and tested in the crystalline seed study, including: (1) a placebo containing the excipients used by Ranbaxy, specifically crospovidone, microcelac 100, and magnesium stearate; (2) a mixture containing 0.1% crystalline valganciclovir hydrochloride; (3) a mixture containing 0.3% crystalline valganciclovir hydrochloride; (4) a mixture containing 0.5% crystalline valganciclovir hydrochloride; and (5) and (6) two tablets provided by Ranbaxy of its valganciclovir hydrochloride. Henck Tr. II 155:5-15; 157:1-7, 158:7-159:1; PTX-577 at R0319832-36; *see also* Henck Tr. II 155:16-158:6; PTX-719 at R0321246-47; PTX-706 (establishing chain for custody of 6 crystalline seed samples tracked by SSCI Laboratory Information Management System (LIMS)).

27. The XRD pattern for the placebo containing only excipients – including magnesium stearate – does not show a peak at 3.5° 2θ. Henck Tr. II 161:8-18; PTX-578 (bottom pattern); PTX-699 at 1. The XRD patterns for the samples containing 0.1%, 0.3%, and 0.5% crystalline valganciclovir hydrochloride each has a peak at 3.5° 2θ. Henck Tr. II 162:8-15; PTX-578 (second, third, and fourth from bottom patterns); PTX-699 at 2-4.

28. In Dr. Henck's opinion to a reasonable degree of scientific certainty, the two Ranbaxy valganciclovir hydrochloride tablets both contained a peak at 3.5° 2θ and, based on a qualitative visual comparison of the 3.5° 2θ peak for both tablets with the peak at 3.5° 2θ of the tablet samples containing 0.1%, 0.3% and 0.5% crystalline valganciclovir hydrochloride, the Ranbaxy tablets each contained crystalline valganciclovir hydrochloride greater than approximately 0.1% by weight. Henck Tr. II 162:16-165:9; PTX-578 (top two patterns); PTX-745; PTX-746.

29. In Dr. Henck's opinion to a reasonable degree of scientific certainty, the peaks at 3.5° 2θ in the two Ranbaxy tablets were not due to magnesium stearate because the placebo, which contained only magnesium stearate and other excipients used by Ranbaxy, does not show a peak at that angle. Moreover, magnesium stearate is only approximately 1% by weight amount in a Ranbaxy tablet while the concentration of valganciclovir hydrochloride API in Ranbaxy's tablets is approximately 62% by weight. Henck Tr. II 166:6-167:7, 171:2-13; Rogers Tr. VI 177:21-178:4; PTX-286 at RVHRX000963.

30. The crystalline seeds promote crystallization of the remaining valganciclovir hydrochloride in Ranbaxy's tablets. Henck Tr. II 167:8-168:22. As Ranbaxy concluded from its moisture uptake studies, "seeds of crystalline contamination" in Ranbaxy's API helped it convert to crystalline form. R. Singh Tr. V 33:25-35:22; PTX-361 at RVHRX0032400-32401. Nevertheless, even if Ranbaxy did not manufacture their tablets with a seed of crystalline material, the tablets would still crystallize when exposed to moisture, because the amorphous state of Ranbaxy's tablets contains high free energy and exposure to moisture facilitates conversion to a crystalline lower free energy state. Henck Tr. II 169:17-171:1.

E. Ranbaxy's Valganciclovir Hydrochloride API Is Hygroscopic And Converts Rapidly To Crystalline Form Upon Exposure To Moisture

31. Ranbaxy's valganciclovir hydrochloride API is "hygroscopic", meaning that it has a tendency to absorb moisture when exposed to the atmosphere, and convert to crystalline form. Chandrashekar Tr. V 137:22-140:8; Khanduri Tr. II 5:1-9 (Video Dep. Tr. 155:10-21); Khanduri Tr. IV 66:10-15, 66:21-67:22, 68:12-71:5, 72:3-73:12, 75:1-5, 76:13-20; Henck Tr. II 117:9-17. If Ranbaxy's valganciclovir hydrochloride is taken out of its packaging and exposed to normal humidity conditions it will convert to crystalline form. Khanduri Tr. II 4:15-25 (Video Dep. Tr. 145:6-146:1); Khanduri Tr. IV 72:22-73:1.

32. Ranbaxy's own data shows that its API converted to crystalline form after being exposed for 3 days to conditions of 40°C and 75% relative humidity, and converted to crystalline form after being exposed for 7 days to room temperature and 45% relative humidity, which are normal ambient conditions. R. Singh Tr. V 29:14-33:24; Chandrashekar Tr. V 77:6-8; PTX-367 at RVHRX0033329; PTX-361 at RVHRX0032400-32401. Ranbaxy's XRD data also shows that its valganciclovir hydrochloride converts to crystalline form when stored in open bottles at standard ambient temperature and relative humidity conditions. Chandrashekar Tr. V 136:4-137:9; PTX-322 at RVHRX0027852.

33. Dr. Khanduri admitted that Ranbaxy's manufacturing process reflects its knowledge that its valganciclovir hydrochloride API is hygroscopic and absorbs moisture when exposed to the atmosphere. Ranbaxy packages its hygroscopic API in three layers of vacuum-sealed polymer bags under nitrogen conditions and with the use of molecular sieves to absorb moisture. The triple-bagged API is then placed in a sealed drum before sending it to Ranbaxy's tablet department. Khanduri Tr. IV 39:21-41:12, 66:10-20; DX-800.05. Moreover, in Ranbaxy's PCT application, Ranbaxy admitted that its valganciclovir hydrochloride must be stored "under nitrogen in the strict absence of atmosphere or other water" in order to prevent the material from crystallizing. Henck Tr. II 119:13-120:11; PTX-303 at 8. Dr. Henck has observed that the API "acts like a sponge" and absorbs water very quickly and easily. Henck Tr. II 115:9-22.

34. Ranbaxy further uses HDPE bottles that are heat sealed in order to protect its tablets from moisture. Henck Tr. II 118:9-14; PTX-286 at RVHRX0001295-96. Ranbaxy's use of molecular sieves and HDPE bottles demonstrates that it is aware that its valganciclovir hydrochloride API is hygroscopic and exposure of its tablets to ambient humidity conditions results in conversion to crystalline form. Henck Tr. II 118:15-119:8.

F. Ranbaxy's Drug Formulation, Excipients And Coating Do Not Prevent The API In Its Tablets From Absorbing Moisture When The Tablets Are Exposed To Ambient Conditions Or Swallowed By Patients

35. The three excipients Ranbaxy uses in its valganciclovir hydrochloride tablets are crospovidone, microcelac 100, and magnesium stearate, none of which protects Ranbaxy's API in the core of the tablet from moisture. N. Singh Tr. II 7:21-8:8 (Video Dep. Tr. 88:19-25); R. Singh Tr. II 7:21-8:8 (Video Dep. Tr. 172:4-10, 173:11-174:19); R. Singh Tr. V 41:3-7, 44:17-45:1, 45:17-46:13; Henck Tr. II 109:21-110:11, 116:13-117:3; PTX-286 at RVHRX0000934. The ingredients Ranbaxy uses in the coating for its valganciclovir tablets are Opadry pink, polyethylene glycol-400, methylene chloride, and acetone. R. Singh Tr. V 46:21-47:5. The purpose of the coating ingredients is for "aesthetics" only, to make the tablets look like Valcyte, and they do not have any attributes of moisture protection. R. Singh Tr. V 46:21-48:25; Henck Tr. II 115:23-116:12, 116:23-117:3.

36. Ranbaxy has taken no precautions to formulate its tablets in a way to prevent its valganciclovir hydrochloride API from absorbing moisture. Henck Tr. II 117:4-8. Ranbaxy has offered no evidence to establish that subjecting its valganciclovir hydrochloride API to compaction makes its API less susceptible to moisture (R. Singh Tr. V 35:24-37:6), and that its dry granulation process produces a more stable API than other manufacturing processes (R. Singh Tr. V 37:7-38:11; Chandrashekar Tr. V 137:10-15). Since Ranbaxy learned of Roche's contention of infringement, Ranbaxy "remained with this formulation. . . [and] do not intend to change" it. R. Singh Tr. V 46:14-20.

IV. AN XRD PEAK AT 3.5° 2Θ IDENTIFIES THE PRESENCE OF VALGANCICLOVIR HYDROCHLORIDE IN CRYSTALLINE FORM

A. Valganciclovir Hydrochloride In Crystalline Form Has A Distinctive Peak At 3.5° 2θ

37. Roche's expert Dr. Henck (PTX-572) testified that in 1994, as today, a person of skill in the art would understand that the presence of a compound "in crystalline form" is detected by an XRD pattern that records "at least one peak." Henck Tr. II 103:16-104:2, 17-22. It is accepted practice among crystallographers to use a single peak in an XRD to identify a known compound. When the ingredients of a sample are known, a single peak can be used to determine whether a specific compound in the sample is in crystalline form. For example, looking at a sample that consists of a mixture of different compounds, and there is one unique peak that can identify a specific compound in the sample where no other peaks occur, then one peak is enough to identify that specific compound. Henck Tr. II 84:19-25, 132:3-9, 133:14-17.

38. Ranbaxy's expert Dr. Rogers agreed that a person of skill in the art can rely on a single XRD peak to identify crystalline material in a sample if the person is provided with additional information concerning the sample's composition. In this case, the excipients, coating, and active ingredient of Ranbaxy's tablets are all known. Rogers Tr. VI 171:4-18; Henck Tr. II 132:10-19.

39. Peer-reviewed scientific literature confirms that the presence of a single distinctive XRD peak is sufficient to identify the presence of a given compound in crystalline form within a mixture of other known materials.[1] The only literature -- the Hanawalt search technique -- presented by Ranbaxy's expert Dr. Cockcroft to the Court on the issue of whether a single peak can be used to detect the presence of a crystalline material is irrelevant, because this technique

[1] Henck Tr. X 129:19-132:3, discussing PTX-752 at 529-30 (Fig. 1) (relying on a single peak at 7.5º 2θ to detect crystalline aspirin and a single peak to 18.0º 2θ to detect crystalline acetaminophen in a sample of the drug Excedrin); Henck Tr. X 132:4-133:24, discussing PTX-768 at 225 (Fig. 6) and PTX-764 (using a single peak at 9º 2θ to identify crystalline compound in a mixture containing 98% amorphous material); Henck Tr. X 133:25-135:1, discussing PTX-769 at 517 (Fig. 1) (using a single peak at 12.4º 2θ to detect the presence of crystalline alpha-lactose monohydrate in mixtures); Henck Tr. X 135:2-136:19, discussing PTX-770 at 4319-21 (Figs. 10 and 12) (any of several peaks sufficient to identify crystalline material).

involves using *more than one* XRD peak to identify *unknown* material. Cockcroft Tr. VII 46:1-47:23; Henck Tr. X 199:19-25. Dr. Cockcroft's testimony on this issue is entitled to little if any weight, because he never reviewed the claims and specification of the '953 patent, has no opinion on the meaning of the claim term "in crystalline form" and has not authored any publications in recognized scientific literature directed to XRD analysis of pharmaceutical products. Cockcroft Tr. VII 40:23-41:7, 45:11-25.

40. Every XRD pattern of crystalline valganciclovir hydrochloride, including Form X and Form Y, contains a peak at 3.5° 2θ, which is used as a "reference peak to determine crystalline valganciclovir hydrochloride." Henck Tr. II 131:15-22. Ranbaxy's expert Dr. Rogers agrees that crystalline valganciclovir hydrochloride always has an XRD peak at 3.5° 2θ (Rogers Tr. VI 169:25-170:5), and testified that he has never seen an XRD pattern of crystalline valganciclovir hydrochloride that did not have an XRD peak at 3.5° 2θ (Rogers Tr. VI 170:6-9). Ranbaxy's expert Dr. Cockcroft also agreed that he has never seen an XRD pattern of crystalline valganciclovir hydrochloride that did not have a peak at 3.5° 2θ. Cockcroft Tr. VII 44:22-45:1.

41. In Dr. Henck's expert opinion, a peak at 3.5° 2θ is the "distinguishing fingerprint" or "signature peak" for identifying valganciclovir hydrochloride in crystalline form. Henck Tr. II 131:23-132:2, 10-19. Ranbaxy's experts, Drs. Rogers and Cockcroft, agree that crystalline valganciclovir hydrochloride has its "most distinctive" and "strongest" XRD peak at 3.5° 2θ. Rogers Tr. VI 169:21-24; Cockcroft Tr. VII 44:3-45:10. Dr. Cockcroft agreed upon inquiry by the Court that in this case "distinctive" peak and "strongest" peak have the same meaning. Cockcroft Tr. VII 45:2-10.

42. The only other ingredient in Ranbaxy's tablets that has a peak around 3.5° 2θ is the excipient magnesium stearate which "has a peak at approximately 3.6 degrees two-theta, which

is one of the weaker peaks in the x-ray diffraction pattern of magnesium stearate." Henck Tr. II 132:20-25. This weak peak does not "interfere" with the ability to identify crystalline valganciclovir hydrochloride in Ranbaxy's tablets. Henck Tr. II 133:1-13.

B. Ranbaxy Agrees With Roche's Expert Dr. Henck That A Peak At 3.5º 2θ Detects The Presence Of Valganciclovir Hydrochloride In Crystalline Form

43. Ranbaxy's Vice President of Global Quality and Analytical Research, Dr. T.G. Chandrashekar, who has "read and interpreted" "thousands" of XRD patterns, including those generated by his department, testified that Ranbaxy has chosen to "detect" the "presence of crystalline valganciclovir hydrochloride" based "solely by an [XRD] peak at 3.5° 2θ " and has done this "since 2005." Chandrashekar Tr. V 61:9-10, 62:3-64:19, 140:9-17. Shalender Gupta, an Analyst at Ranbaxy, also testified that "an XRD peak at 3.5° 2θ " indicates the "presence of crystalline valganciclovir hydrochloride." Gupta Tr. II 5:10-17 (Video Dep. Tr. 108:6-12).

44. Both of Ranbaxy's experts Drs. Rogers and Cockcroft acknowledged that Ranbaxy relies "solely" on a peak at 3.5° 2θ to detect the presence of valganciclovir hydrochloride in crystalline form and that this is the same approach that Roche's expert, Dr. Henck, used in his tests on Ranbaxy's tablets to determine the presence of crystalline valganciclovir hydrochloride. Rogers Tr. VI 171:25-173:1; Cockcroft Tr. VII 49:3-24. In fact, Ranbaxy's expert, Dr. Rogers, conceded that Ranbaxy's approach "is a conservative approach." Rogers Tr. VI 173:9-20. Moreover, both Drs. Rogers and Cockcroft admitted that they had much less experience in analyzing valganciclovir hydrochloride by XRD than Ranbaxy. Dr. Rogers testified that he has never undertaken any XRD analyses of Ranbaxy's valganciclovir hydrochloride, while Ranbaxy has "done this for many years" (Rogers Tr. VI 173:21-174:6) and Dr. Cockcroft testified that he has only analyzed Ranbaxy's valganciclovir hydrochloride tablets by XRD "two times," in

contrast to Ranbaxy's employees, who have "done it may more times than I have" and have "more experience" (Cockcroft Tr. VII 49:25-51:10).

45. Ranbaxy's Standard Test Procedure (PTX-338) for analyzing batches of its API relies on the presence of a peak at 3.5° 2θ as the sole criterion for identifying crystalline valganciclovir hydrochloride (Chandrashekar Tr. V 131:22-25; Henck Tr. II 127:19-129:3, 139:9-140:5, 132:10-19) and to "determin[e] low levels of contamination, if any, of crystalline valganciclovir hydrochloride" because the "peak at 3.5 [°2θ] is distinct and has the maximum intensity compared to all the other distinctive peaks observed in the pattern" (Chandrashekar Tr. V 85:24-87:11; DX-84 at RVHRX0030933; DX-802.04).

46. Ranbaxy's Standard Test Procedure (PTX-339) for detecting the presence of crystalline valganciclovir hydrochloride in its tablets also relies solely on the presence of a peak at 3.5° 2θ. Chandrashekar Tr. V 131:14-21; DX-382; DX-802.13. PTX-290 provides further evidence that Ranbaxy relies solely on an XRD peak at 3.5° 2θ to detect the presence of crystalline valganciclovir hydrochloride. The words "Qualitatively crystalline content clearly detected" written by a Ranbaxy employee are next to two XRD analyses and refer to a peak at 3.5° 2θ . Rogers Tr. VI 174:7-175:8; PTX-290.

47. In its PCT application, Ranbaxy uses the words "crystalline form," the same words as Claim 1 of the '953 patent, to describe the crystalline portion of a mixture of crystalline and amorphous valganciclovir hydrochloride, as detected by XRD. Henck Tr. II 97:13-98:24; PTX-303 at 3; FIG. 3.

C. The Assertion Of Ranbaxy's Expert Dr. Rogers That "Form A" And "Form B" Are Partially Ordered Is Meritless

48. Ranbaxy agrees that valganciclovir hydrochloride exists in two polymorphic forms – crystalline and amorphous. Rogers Tr. VI 156:21-159:2. In a mixture containing both

crystalline and amorphous forms, the crystalline portion will have three-dimensional order which will diffract x-rays causing XRD peaks. Rogers Tr. VI 155:15-156:20.

49. Valganciclovir hydrochloride Forms X, Y, A, and B each has a prominent XRD peak at 3.5° 2θ . Rogers Tr. VI 169:16-20; Henck Tr. II 134:7-135:10, 140:10-142:7; PTX-33 at R0123658, 662, 663. In its March 1996 "RS-79070-194 Preformulation Book," Roche described valganciclovir hydrochloride Form A as a "semi-amorphous, flake-like material" that is "not stable under ambient conditions" and "converted to Form X" under accelerated conditions of 98% relative humidity for three days. DX-104 at R0115910; Rogers Tr. VI 168:9-21. Roche described Form B as a "gelatinous amorphous material" that is "not stable under ambient conditions" and "converted to a crystalline form." DX-104 at R0115910; Rogers Tr. VI 168:22-25; Henck Tr. II 142:8-143:1.

50. In its 2000 New Drug Application for its Valcyte tablets, Roche summarized its polymorphism studies on valganciclovir hydrochloride, and stated that "Early in the development process, two metastable forms originally called A and B were thought to be present. However, these appear to be merely amorphous material containing low amounts of crystalline material." DX-209 at R0000158; Rogers Tr. VI 165:1-167:8; Henck Tr. III 141:15-142:8.

51. Nowhere in the expert reports of Ranbaxy's expert Dr. Rogers or in his deposition did he opine that the valganciclovir hydrochloride API in Ranbaxy's tablets is "partially ordered" or set forth any evidence of a "partially ordered" structure for valganciclovir hydrochloride. Rogers Tr. VI 152:1-154:1. Dr. Rogers also "did not undertake any test of the crystal structure of valganciclovir hydrochloride" (Rogers Tr. VI 154:13-18), including analyses of the crystalline structure of Ranbaxy's tablets that were the subject of Dr. Henck's medical pill tray organizer and simulated gastric fluid studies (Rogers Tr. VI 197:20-198:7). Dr. Rogers did not cite to a

single document indicating that the valganciclovir hydrochloride API in Ranbaxy's tablets is "partially ordered" (Rogers Tr. VI 154:19-22), nor did he cite to a single peer-reviewed journal or text describing "partially ordered" pharmaceutical materials (Rogers Tr. VI 154:23-155:2).

52. Ranbaxy's expert Dr. Cockcroft testified that valganciclovir hydrochloride Forms A and B contain approximately one percent crystalline valganciclovir hydrochloride "based on the diffraction data presented" to him. Cockcroft Tr. VII 68:4-17.

D. The Assertions Of Ranbaxy's Experts Drs. Rogers And Cockcroft That Crystalline Valganciclovir Hydrochloride Has A Multi-Peak "Fingerprint" Including Additional Peaks At 9.5 And 11.8° Two Theta Are Meritless

53. Every XRD pattern of crystalline valganciclovir hydrochloride, including Form X and Form Y, contains a peak at 3.5° 2θ (FF 40), while the presence or absence of peaks at other angles can vary. Numerous factors can affect the number of peaks in a pattern and the height, width and position of a peak, including but not limited to, preparation of the sample, how the sample was obtained and other components in the sample. Henck Tr. II 91:24-93:14.

54. Samples of both the X and Y Forms of pure crystalline valganciclovir hydrochloride prepared with isopropanol solvent exhibit a peak at 3.5° 2θ and also contain peaks at 9.5°, 11.8°, 14.7°, 15.6°, and 17.1° 2θ. Henck Tr. II 134:7-135:21; PTX-33 at B1-11. A sample of crystalline valganciclovir hydrochloride prepared with a different solvent, ethanol, rather than isopropanol still results in a peak at 3.5° 2θ, but only has weak peaks at 9.5° and 14.7° 2θ and no peaks at 11.8°, 15.6°, and 17.1° 2θ. Henck Tr. II 135:22-137:10; PTX-281A. In another sample of crystalline valganciclovir hydrochloride obtained from an ethanol solvent and then exposed to ambient conditions for two hours, the XRD pattern has a peak at 3.5° 2θ and weak peaks at 9.5° and 11.8° 2θ and no peaks at 14.7°, 15.6°, and 17.1° 2θ. Henck Tr. II 137:11-138:14; PTX-282A.

55. In the Form X and Y samples of crystalline valganciclovir hydrochloride prepared with isopropanol and the two samples of crystalline valganciclovir hydrochloride prepared with ethanol (PTX-281A and PTX-282A), the common peak found in all the samples is at 3.5° 2θ. Henck Tr. II 139:4-8; PTX-33. Ranbaxy's experts Drs. Rogers and Cockcroft also agreed that XRD patterns PTX-281A and PTX-282A of valganciclovir hydrochloride prepared with ethanol do not include peaks at 9.5 and 11.8° two theta. Rogers Tr. VI 196:25-197:14, Cockcroft Tr. VII 60:15-62:5.

V. THE SALE OF RANBAXY'S TABLETS WILL INDUCE INFRINGEMENT OF THE '953 PATENT BY PATIENTS FOR WHOM THE DRUG IS PRESCRIBED

A. The API In Ranbaxy's Tablets Converts To Crystalline Form Under Normal Conditions Used By Patients, Making The Patients Direct Infringers

1. The Majority Of The API In Ranbaxy's Tablets Converts To Crystalline Form When Stored In Medical Pill Tray Organizers

a. AIDS And Organ Transplant Patients Will Store Ranbaxy's Tablets In Medical Pill Tray Organizers

56. Solid organ transplant and AIDS patients must take numerous medications on a daily basis and at varying times of the day. To help take these medications at the proper times every day, solid organ transplant and AIDS patients commonly store their tablet medications in medical pill tray organizers of the type illustrated in PTX-573 and PTX-715, which typically hold pills for seven days a week with multiple compartments for each day representing different daily medication times. Snydman Stip. ¶2; Drew Tr. I 86:7-87:14, 87:20-88:6, 88:7-23; Marangio Tr. I 154:18-155:15; Wong Tr. I 133:21-134:21.

57. Valcyte is one of the drugs commonly prescribed to AIDS patients with CMV retinitis and solid organ transplant patients. These patients typically store their Valcyte tablets, along with their other tablet medications, in medical pill tray organizers such as the pill tray shown in PTX-573 and PTX-715. Snydman Stip. ¶3; Drew Tr. I 89: 6-13 ("essentially 100 percent" of

AIDS patients taking Valcyte store their medications in pill trays such as PTX-715); Marangio Tr. I 158:6-9 ("everyone in the industry" educating AIDS patients recommends the use of pill tray organizers) and 162:6-21 (all advanced stage AIDS patients, such as those taking Valcyte, use pill tray organizers). It is standard medical practice to remove pills from individual medicine bottles and load the pill tray once per week. Snydman Stip. ¶3; Drew Tr. I 88:7-11.

58. If a generic version of valganciclovir hydrochloride were approved and placed on sale in the United States, it would be substituted for Valcyte and used and handled in the same way as Valcyte. Thus, AIDS and solid organ transplant patients would typically store a generic version of valganciclovir hydrochloride for up to a week at a time in pill trays in the same manner as Roche's Valcyte. Snydman Stip. ¶4; Drew Tr. I 89:21-90:3; Marangio Tr. I 156:8-157:4; Wong Tr. I 134:19-135:5.

b. The Valganciclovir Hydrochloride API In Ranbaxy's Tablets Converts To Crystalline Form Within 24 To 48 Hours After Being Stored In A Medical Pill Tray Organizer

59. Dr. Henck supervised a medical pill tray organizer study in his laboratory that involved the storage of Ranbaxy's valganciclovir hydrochloride tablets in a pill tray organizer that held pills for a seven-day week. Henck Tr. III 29:1-16; PTX-573; *see also* Henck Tr. III 33:25-37:9; PTX-718 at R0319837-76; PTX-574; PTX-719 at R0321261, R0321248-60; PTX-711, PTX-581, (PTX-698 at 1-8), PTX-582 (PTX-698 at 9-16), PTX-583 (PTX-698 at 17-24), PTX-584 (PTX-698 at 25-32), PTX-585 (PTX-698 at 33-40) (establishing chain of custody for 80 Ranbaxy tablets used in this study).

60. Based on the dosage instructions on Ranbaxy's package insert, two 250 milligram tablets were placed in a pill tray compartment for each day of the week. The pill bottle was then resealed with the desiccant left inside and placed in a stability chamber in the laboratory set to 25°C and 60% humidity, which are the conditions recommended by the Int'l Conf. for

Harmonization to represent indoor conditions in the U.S. Henck Tr. III 29:17-31:7, 32:7-17; PTX-718 at R0319837-76; PTX-573; PTX-694. Throughout the study, the laboratory in which the pill tray was kept was at 20-25°C and 50-75% relative humidity (hereinafter, "ambient conditions"). There was no need for modifications to climate conditions because "[t]he conditions in the lab are. . . comparable to the ones in the climate chamber." Henck Tr. III 32:18-33:3, 85:6-15; PTX-765.01.

61. Each week an XRD analysis was performed on a tablet straight from the bottle. Then, on each day of the week, a tablet was taken from the medical pill tray organizer and subjected to XRD analysis. The experiment was repeated for five weeks. Henck Tr. III 29:17-31:7, 32:7-17; PTX-718 at R0319837-76; PTX-573; PTX-694. For the XRD analyses, each tablet was first rendered, not ground, into a powder in ambient conditions in the laboratory by lightly crushing it in a mortar and pestle, which does not change the chemical composition of the tablet, "immediately after they were removed from the pill tray organizer." Henck Tr. III 32:18-33:17; Henck Tr. X 139:11-141:6, 142:25-144:3; PTX-718 at R0319838; PTX-765.01; PTX-765.03.

62. In Week 1 of the medical pill tray organizer study, a peak at 3.5° 2θ appeared in the Day 2 tablets, indicating the presence of crystalline valganciclovir hydrochloride within 48 hours of exposure to ambient conditions. The tablets for every subsequent day also showed a peak at 3.5° 2θ, indicating the presence of crystalline valganciclovir hydrochloride. Henck Tr. III 37:14-40:2, 42:2-8, PTX-581; PTX-698 at 1-8.

63. In Week 2, a peak at 3.5° 2θ appeared in the Day 1 tablets, indicating the presence of crystalline valganciclovir hydrochloride within 24 hours of exposure to ambient conditions. The tablets for every subsequent day also showed a peak at 3.5° 2θ, indicating the presence of crystalline valganciclovir hydrochloride. Henck Tr. III 42:9-43:14; PTX-582; PTX-698 at 9-16.

64. Weeks 3, 4, and 5, also show a peak at 3.5° 2θ indicating the presence of crystalline valganciclovir hydrochloride within 24 to 48 hours of exposure to ambient conditions. Henck Tr. III 43:15-21; PTX-583 (PTX-698 at 17-24), PTX-584 (PTX-698 at 25-32), PTX-585 (PTX-698 at 33-40).

65. Based on the medical pill tray organizer study, in Dr. Henck's expert opinion to a reasonable degree of scientific certainty, within 24 to 48 hours after Ranbaxy's tablets are exposed to ambient conditions, the vast majority of the valganciclovir hydrochloride in those tablets converts to crystalline form. Henck Tr. III 144:4-145:18; PTX-698. During the study, Dr. Henck observed that after 24 to 48 hours the surface color of Ranbaxy's tablets started to become opaque and the coating began to crack. Dr. Henck attributed the cracking and change in appearance of Ranbaxy's tablets to crystallization. Henck Tr. III 43:22-45:16; DX-708A. Dr. Rogers agreed that "some crystals" of valganciclovir hydrochloride may have formed in Ranbaxy's tablets that were the subject of Dr. Henck's medical pill tray organizer study. Rogers Tr. VI 199:21-200:2.

2. At Least A Majority Of The API In Ranbaxy's Tablets Converts To Crystalline Form Within 30 Seconds To 8 Minutes After Swallowed By Patients

66. Ranbaxy's ANDA package insert states that its tablets are for "oral administration." Henck Tr. II 121:12-19; PTX-286 at RVHRX0000127.

67. Roche's expert Dr. Henck supervised a simulated gastric fluid (SGF) study involving placing 7 Ranbaxy tablets one at a time in a basket, United States Pharmacopeia (USP) Apparatus 1, in order to hold each tablet, and then the basket was lowered for a specific time interval into SGF rotated by a paddle, USP Apparatus 2. After exposure to SGF for a specified time period, the tablet was submitted for XRD analyses. Henck Tr. III 4:5-7, 4:15-7:5, 7:23-9:4, 9:7-10:5; PTX-466, PTX-696, PTX-697; *see also* Henck Tr. III 12:17-15:19, 15:25-16:3; PTX-

707; PTX-719 at R0321261-63; PTX-718 at R0319878-79 (establishing chain of custody for 7 Ranbaxy tablets).

68. Roche's gastroenterology expert, Dr. Feldman (PTX-465), reviewed the SGF study to determine whether the study simulates what would be expected to occur in the human stomach after a Ranbaxy tablet is swallowed. Feldman Tr. II 22:25-23:19. Ranbaxy did not offer a medical expert to rebut Dr. Feldman's testimony.

69. Dr. Feldman confirmed that the SGF in Dr. Henck's study: (i) followed the "Gastric Fluid, Simulated, TS" entry in the USP, which is the recommended recipe for simulated human gastric fluid (Feldman Tr. II 28:25-29:13; Henck Tr. III 10:6-23; PTX-575 at 82; PTX-467); (ii) used concentrations of hydrochloric acid, pepsin, and sodium well within the physiological range in human gastric fluid (Feldman Tr. II 30:9-16; PTX-467); (ii) used the physiological pH of 1.2 (Feldman Tr. II 23:17-24:18, 29:6-15, 30:17-32:6; Henck Tr. III 10:6-23; PTX-575; PTX-467; DX-164; PTX-469); and (iv) was maintained at 37°C body temperature (Feldman Tr. II 32:7-25; PTX-575 at 82). Dr. Feldman further concluded that combining the basket of USP Apparatus I and paddle of USP Apparatus II was appropriate (Feldman Tr. II 27:2-28:6; PTX-575 at 82; PTX-466 at 278 (USP instructs to "[u]se the assembly from Apparatus I" with Apparatus II)) and that Dr. Henck used a paddle rotation of 50 RPM, within the recommended range of 50 to 75 RPMs (Feldman Tr. II 28:8-24; PTX-575 at 82).

70. In Dr. Feldman's expert opinion to a reasonable degree of medical certainty: (i) Dr. Henck's gastric fluid study simulated the conditions in the human stomach (Feldman Tr. II 33:20-34:10, 35:16-21); (ii) the concentrations of components in Dr. Henck's SGF are the same as in human gastric fluid (Feldman Tr. II 35:9-15); (iii) a Ranbaxy tablet ingested by a patient would undergo the same conditions simulated by Dr. Henck's study (Feldman Tr. II 35:22-36:2);

and (iv) he has no reason to think that any of the inactive ingredients in a Ranbaxy tablet would react with any chemical in the SGF (Feldman Tr. II 36:16-22).

71. The Ranbaxy tablet placed in SGF for only 30 seconds showed a "strong" peak at 3.5° 2θ, reflecting the presence of crystalline valganciclovir hydrochloride. Henck Tr. III 16:13-17:10, 19:14-20:2; PTX-576; PTX-700 at 2. The Ranbaxy tablets placed in SGF for one, two, four, and eight minutes also all show a peak at 3.5° 2θ, reflecting the presence of crystalline valganciclovir hydrochloride. The tablet in the fluid for fifteen minutes disintegrated. Henck Tr. III 17:11-18:18, 19:14-20:2; PTX-576; PTX-700 at 3-7.

72. In Dr. Henck's expert opinion to a reasonable degree of scientific certainty, after Ranbaxy's tablets are swallowed by a patient and exposed to gastric fluid in a patient's stomach, the vast majority of the valganciclovir hydrochloride API converts rapidly to crystalline form. Henck Tr. III 20:3-22:1, 23:6-21, 146:7-147:4; PTX-700; *see also* Henck Tr. III 3:19-4:4, 4:8-14.

73. Ranbaxy's expert Dr. Rogers' analysis of the peak data generated from Dr. Henck's SGF study confirms peaks at 3.5° 2θ for the tablet samples tested at 30 seconds, one minute, two minutes, four minutes, and eight minutes. DX-803.27; Rogers Tr. VI 195:22-196:9. Both Dr. Henck's and Dr. Rogers' analyses of the XRD data from Dr. Henck's SGF study confirms that at least a majority of the valganciclovir hydrochloride API in Ranbaxy's tablets converted to crystalline form. Henck Tr. X 147:11-148:6; *compare* PTX-700 *with* DX-803.27. Dr. Rogers agreed that "some crystals" of valganciclovir hydrochloride may have formed in Ranbaxy's tablets that were the subject of Dr. Henck's SGF study. Rogers Tr. VI 198:8-199:3.

3. Ranbaxy Failed To Rebut Dr. Henck's Tests Showing That Ranbaxy's Tablets Will Infringe When Used In The Normal Manner By Patients

a. Ranbaxy's Expert Dr. Rogers Did No Tests Of His Own

74. Ranbaxy's expert Dr. Rogers did not undertake any XRD analyses of Ranbaxy's tablets stored in medical pill tray organizers or subjected to SGF, nor is he aware of anybody from Ranbaxy that undertook such tests. Rogers Tr. VI 190:5-19. Ranbaxy never carried out any stability studies of its tablets stored in a pill tray or simulating the effect of being swallowed by a patient and then testing by XRD to determine if the tablets converted to crystalline. R. Singh Tr. V 23:3-7, 28:12-29:13; Chandrashekar Tr. V 137:10-21.

75. All of Dr. Rogers' analyses of Ranbaxy's data and Dr. Cockcroft's data were of tablets that were stored in the bottle and/or subjected to a nitrogen environment, not to ordinary indoor conditions. Dr. Rogers never personally tested Ranbaxy's or Roche's valganciclovir hydrochloride tablets by XRD, nor did he render any opinion concerning XRDs of Ranbaxy's valganciclovir hydrochloride tablets that were taken out of the bottle and exposed to ambient conditions. Rogers Tr. VI 188:2-6, 188:20-189:23.

b. Dr. Cockcroft's Testing Of Ranbaxy's Tablets Is Not Relevant

76. Ranbaxy's expert Dr. Cockcroft never analyzed Ranbaxy's valganciclovir hydrochloride API or tablets exposed to ambient conditions for any length of time. Cockcroft Tr. VII 51:11-22, 52:16-21, 55:21-56:5. Dr. Cockcroft agrees that solid organ transplant and AIDS patients who will take Ranbaxy's tablets will not expose those tablets to nitrogen gas conditions before taking them, as he did in his analyses. Cockcroft Tr. VII 56:6-24, 57:1-7, 57:14-17.

c. Ranbaxy's Criticisms Of Dr. Henck's Medical Pill Tray Organizer Study Are Meritless

77. Ranbaxy's expert Dr. Rogers did not "undertake any reanalysis of the underlying peak data" for the XRDs in the five weeks of Dr. Henck's medical pill tray organizer study. Nor did Dr. Rogers critique the underlying peak data for any of the peaks appearing at 3.5° 2θ in the XRDs of Dr. Henck's study. Henck Tr. X 138:2-139:10; Rogers Tr. VI 200:3-9; DX-603.

Ranbaxy's expert Dr. Cockcroft did not provide any opinions concerning Dr. Henck's pill tray study. Cockcroft Tr. VII 63:23-64:1.

78. Dr. Rogers' assertion that the rendering of the tablets into powders, which increased the surface area of the components in the tablets exposing them to moisture in the atmosphere, is what induced crystallization, is belied by Dr. Henck's testing 10 tablets at "time zero" to show that the sample preparation methodology does not induce crystallization. Indeed, Dr. Rogers did not criticize Dr. Henck's methodology used or the resulting XRD patterns of these "time zero" tablets. Moreover, the XRD patterns of 8 tablets tested after being stored in a pill tray for 24 hours provides additional support that Dr. Henck's methodology of rendering the tablets into a powder did not induce crystallization. Henck Tr. III 33:4-10; Henck Tr. X 139:11-141:6, 144:16-22; PTX-698; PTX-581; PTX-582; PTX-583; PTX-584; PTX-585; PTX-765.01.

79. Dr. Henck did not remove the Opadry coating from the tablets tested because it would have had a significant impact on the quality of the XRD analysis of the sample, particularly when, as Dr. Henck observed, components in the core of Ranbaxy's tablets adhere to the coating. Henck Tr. X 141:7-142:2; PTX-765.02. Dr. Henck's "time zero" XRD tests further show that the Opadry coating in Ranbaxy's tablets does not contribute to an XRD peak at 3.5° 2θ . Henck Tr. X 142:3-7; PTX-698; PTX-581; PTX-582; PTX-583; PTX-584; PTX-585; PTX-765.02.

80. Dr. Henck's medical pill tray organizer study involved testing 80 tablets. He tested two tablets every week at "time zero" for five weeks and tested 70 other individual tablets, which "gives you much more available information. . . compared to running multiple powder patterns on one sample." Henck Tr. X 142:8-24; PTX-698; PTX-765.02.

81. Dr. Henck's medical pill tray organizer study qualitatively determined the conversion of Ranbaxy's API to crystalline valganciclovir hydrochloride. The use of an arbitrary y-scale is a

well accepted method for comparing XRD patterns, as in this case, where the XRD patterns of 80 tablets were compared. Henck Tr. X 144:4-15; PTX-765.03; *see also* Henck Tr. X 135:2-136:1; PTX-770 at FIG. 10 (a peer reviewed and industry recognized article disclosing XRD patterns with an arbitrary Y scale). Ranbaxy itself "qualitatively" detects crystalline content. FF 46.

82. In both the medical pill tray organizer and SGF studies, the weak peak of magnesium stearate at 3.6° 2θ does not interfere with the ability to identify crystalline valganciclovir hydrochloride by a peak at 3.5° 2θ because "the only material that changes" is valganciclovir hydrochloride converting to crystalline form and causing the peak at 3.5° 2θ, not the crystalline magnesium stearate which is present from the beginning. Henck Tr. II 132:20-133:13. Even Ranbaxy's expert Dr. Rogers conceded that the weak XRD peak for magnesium stearate at 3.6° 2θ in Ranbaxy's tablets "would not be changing over time" in the samples of Ranbaxy's tablets tested by Dr. Henck in his pill tray and SGF studies. Rogers Tr. VI 177:7-20, 194:11-195:21.

d. Ranbaxy's Criticisms Of Dr. Henck's SGF Study Are Meritless

83. Dr. Rogers' analysis of the raw peak data of Dr. Henck's SGF study confirms peaks at 3.5° 2θ for the tablet samples tested at 30 seconds and 1, 2, 4 and 8 minutes, and does not change the conclusion that Ranbaxy's tablets crystallized. DX-803.27; Rogers Tr. VI 195:22-196:9; Henck Tr. X 144:23-145:25; DX-603. Dr. Rogers' analysis of the raw peak data of Dr. Henck's SGF study also confirms the conclusion that at least a majority of Ranbaxy's valganciclovir hydrochloride API converted to crystalline form. Henck Tr. X 147:11-148:6. Dr. Cockcroft did not provide any opinions concerning Dr. Henck's SGF study. Cockcroft Tr. VII 63:19-22.

84. Ranbaxy's position that exposing its tablets to ambient conditions after they were removed from the SGF before testing for XRD induced crystallization is unsupported by the record. The higher temperature and presence of water in the human stomach makes it a more

favorable environment for Ranbaxy's tablets to convert to crystalline form. Henck Tr. III 151:21-152:10. The crystallization rate of Ranbaxy's API in ambient conditions within 24-48 hours is orders of magnitude less than the crystallization rate caused by the warm, moist conditions in the stomach, in which conversion occurs within 30 seconds of exposure to SGF. Henck Tr. X 153:20-155:18; PTX-766.01. The ambient conditions "do not contribute to a crystallization of valganciclovir hydrochloride in the time of the preparation of the samples." Henck Tr. X 153:21-154:13, 207:20-208:2.

85. Each tablet taken from the SGF was submitted for XRD analysis immediately. The preparation of the sample tablets in Dr. Henck's simulated gastric study took approximately 15 minutes, and included cleaning the sample preparation area, setting up a cleaned transmission sandwich holder (TSH) inner metal ring and Etnom thin film to hold sample, transferring the sample to the film and holder, putting the holder into the diffractometer, logging onto the instrument computer software, loading the sample, and running the scan program. The preparation was performed by "highly specialized personnel. . . [who] are highly trained" in accordance with good manufacturing practice (GMP) standards. Henck Tr. X 155:19-157:12; PTX-766.02. The sample preparation time in the SGF study was a little longer than the sample preparation time in the medical pill tray organizer study because a different XRD instrument was used. Henck Tr. X 157:13-158:7.

86. The tablets tested were "drip-dried and lightly ground to a fine powder with an agate mortar and pestle" in ambient conditions after collection and prior to XRD submission. The XRD analyses of tablets tested at "time zero" further show that rendering the tablets into a powder under ambient conditions does not contribute to crystallization of the API. Henck Tr. III 5:23-6:4; Henck Tr. X 158:8-159:4; PTX-718 at R0319878; PTX-700 at 1; PTX-766.03.

87. Contrary to Ranbaxy's assertion, the 8-minute tablet sample was not independently scaled compared to the other tablet samples in the XRD analyses of Dr. Henck's SGF study, but "was normalized in a way like all the other powder patterns in this study." Henck Tr. X 159:5-16, 182:7-18. Ranbaxy's criticism of Dr. Henck's normalization technique for his XRD analyses in the SGF study is unsupported by the record. When XRD patterns are normalized, the relative intensity of the highest intense peak is set at 100 percent and the relative intensities of all of the other peaks in the pattern are scaled relative to that peak. Henck Tr. X 186:7-14. Normalization does not have any effect on the ability of a person of ordinary skill in the art to qualitatively determine whether a peak at 3.5° 2θ for crystalline valganciclovir hydrochloride is present: "whichever way you represent the data, whether you choose to use the raw data or you choose to use normalized x-ray diffraction powder patterns, there is always a peak at 3.5 degrees two theta." Henck Tr. X 145:16-25, 147:1-10, 206:1-16. Normalization is a proper technique when comparing XRD patterns for samples, such as during the SGF study where "we partially dissolve the coating, for example, and partially the outer core of the tablet will start to dissolve, which means we have different types of samples." Henck Tr. X 146:1-18, 184:20-185:1.

88. The record shows that Ranbaxy normalizes its own XRD data. For example, Ranbaxy normalized the peak data in the XRD analyses of its tablet placebo and a tablet from Exhibit batch #1557337. This normalization is shown in the column labeled "Rel. Int.[%]" in the peak lists for these XRD analyses. Henck Tr. X 167:18-169:13; DX-551 at RVHRX0031527; DX-552 at RVHRX0031514.

89. Ranbaxy's litigation contrived "entropy theory" purports that its tablets do not convert into crystalline form prior to dissolving because this would allegedly violate the "law of thermodynamics." However, none of Ranbaxy's experts opined at trial or in their expert reports

that conversion of the API in Ranbaxy's tablets to crystalline form when placed in solution would violate the law of thermodynamics (R. Singh Tr. V 10:6-19) and none of the documents relied upon by Ranbaxy in this case support or even mention Ranbaxy's "entropy theory" (R. Singh Tr. V 12:10-16).

90. Dr. Henck observed in his SGF study that the valganciclovir hydrochloride "material crystallizes before it dissolves." Henck Tr. X 152:16:153:6; PTX-700; PTX-576. In Dr. Henck's expert opinion to a reasonable degree of scientific certainty, it is a common understanding in the scientific community and described in the scientific literature that an amorphous material crystallizes very rapidly before dissolving, so that the dissolution curve of an amorphous material will match up with that of a crystalline material. Henck Tr. III 152:11-153:14; PTX-286 at RVHRX0002073.

e. Ranbaxy's Criticisms Of Dr. Henck's Crystalline Seed Study Are Meritless

91. Dr. Rogers' analysis of the raw peak data from Dr. Henck's crystalline seed study confirms the presence of an XRD peak at 3.5° 2θ in the two Ranbaxy tablets tested. Henck Tr. X 159:17-161:19, 170:12-171:7; PTX-745; PTX-746; PTX-578; PTX-699; DX-803.22; DX-803.23; DX-603. Dr. Rogers admitted that Ranbaxy's Tablet No. 2 in Dr. Henck's study has an XRD peak at 3.5° 2θ . DX-803.23; Rogers Tr. VI 192:8-17. Dr. Cockcroft did not provide any opinions concerning Dr. Henck's crystalline seed study. Cockcroft Tr. VII 62:25-63:18.

92. Roche's expert Dr. Henck's conclusion of the presence of a small amount of crystalline valganciclovir hydrochloride, based on a qualitative visual analysis of a peak at 3.5° 2θ for the two Ranbaxy tablets tested compared to a peak at 3.5° 2θ in the samples containing 0.1%, 0.3%, and 0.5% crystalline valganciclovir hydrochloride, is in accordance with FDA pharmaceutical industry guidelines for validating analytical methods, which advise that "[v]isual inspection may

be used for noninstrumental methods but may also be used with instrumental methods." PTX-763 at 7. Based on these FDA guidelines, a person of skill in the art would be able to analyze the XRD patterns in Dr. Henck's crystalline seed study and determine a limit of detection by visual inspection. Henck Tr. III 105:3-18; Henck Tr. X 163:6-167:17, 172:22-173:9; PTX-767.03. Ranbaxy itself "qualitatively" detects crystalline content. FF 46.

93. The fact that the XRD analyses in Dr. Henck's crystalline seed study were conducted over a period of three and half months did not change the physical or chemical stability of the samples. The instruments used were calibrated and operated under GMP standards. Furthermore, the laboratory notebook pages underlying this study indicate that proper sample preparation and storage methods were used, including storing the placebo excipient mixture in a glass scintillation vial, and each of the 0.1%, 0.3%, and 0.5% crystalline standards in a capped vial. The Ranbaxy tablet samples were each "lightly crushed" and "immediately" submitted for XRD analysis. Henck Tr. II 154:12-16; Henck Tr. X 171:8-172:21; PTX-577 at R0319832-34; PTX-767.01.

94. Dr. Henck's laboratory notebook also indicates that the excipients used to make the analytical placebo in Dr. Henck's crystalline seed study were measured in the amounts disclosed in Ranbaxy's Standard Test Procedure for its tablets and mixed in a Turbula for geometric mixing, which is "the best way to get a homogeneous sample" and then sifted according to Ranbaxy's test procedure. The 0.1%, 0.3%, and 0.5% crystalline standards were made by geometrically combining valganciclovir hydrochloride and the excipient blend using the core and quarter technique. Henck Tr. X 174:9-17; PTX-577 at R0319832-34; PTX-767.04.

95. The excipients used in this study were the same excipients used by Ranbaxy and were obtained from industry-recognized pharmaceutical suppliers, Meggli (microcelac 100), Fischer

(magnesium stearate), and Fluka (crospovidone). These manufacturers are identified in the laboratory notebook pages underlying this study. Henck Tr. X 174:18-175:9; PTX-577 at R0319832-34.

96. Ranbaxy's Standard Test Procedure, which Dr. Henck's laboratory followed to conduct the crystalline seed study, does not require any "statistical analysis," "limit of detection analysis," "calibration curve analysis" or "signal-to-noise analysis." Henck Tr. III 147:5-24; PTX-339. Ranbaxy's expert Dr. Rogers did not undertake any XRD analyses of Ranbaxy's tablets applying Ranbaxy's Standard Test Procedure for detecting crystalline valganciclovir hydrochloride. Rogers Tr. VI 190:20-191:6; PTX-339.

97. The weak XRD peak at 3.6° 2θ for magnesium stearate in Ranbaxy's tablets is not detectable. Not only is this confirmed by Ranbaxy's own XRD analyses of its tablet placebo, it is confirmed by Dr. Henck's placebo XRD analysis in his crystalline seed study, which does not show a peak at 3.6° 2θ or 5.4° 2θ. Henck Tr. X 169:14-170:11; PTX-699; DX-551. Ranbaxy's expert, Dr. Rogers, agreed that the XRD pattern for the placebo analyzed in Dr. Henck's crystalline seed study does not have a peak at 3.5° 2θ . Rogers Tr. VI 192:18-193:2.

98. Despite the fact that Ranbaxy's tablets contain the excipient magnesium stearate, which has an XRD peak at 3.6 ° 2θ, Ranbaxy's Standard Test Procedure for detecting crystallinity in its tablets focuses only on a peak at 3.5° 2θ for detecting crystalline valganciclovir hydrochloride. Rogers Tr. VI 176:8-13; Chandrashekar Tr. V 132:1-7; DX-382 at RVHRX0039258-60.

99. Ranbaxy's Analytical Department generated XRD data for its own tablet placebo, which includes magnesium stearate. Ranbaxy's expert Dr. Rogers agreed that neither the XRD nor the corresponding peak list indicates a peak at 3.5° 2θ for magnesium stearate. Rogers Tr. VI 176:15-177:4; Chandrashekar Tr. V 132:8-133:10; DX-551. Ranbaxy's expert Dr. Cockcroft

also agreed that Ranbaxy did not identify any peak at 3.5 or 3.6° 2θ for magnesium stearate, testifying that "the software certainly didn't pick it up in an automatic peak search mode." Cockcroft Tr. VII 64:12-23.

100. In Dr. Cockcroft's overlay comparing his XRD analysis of a tablet made with crystalline valganciclovir hydrochloride to the XRD of Ranbaxy's placebo, Dr. Cockcroft agreed that the XRD of the tablet does not clearly indicate the presence of magnesium stearate. Cockcroft Tr. VII 64:24-66:2; DX-558. Ranbaxy's Analytical Department also generated XRD data for its tablets, as shown in DX-552, which Ranbaxy's expert Dr. Rogers agreed does not show a peak at 3.5° 2θ for magnesium stearate. Rogers Tr. VI 94:20-25; DX-552; DX-549; DX-803.19.

f. An Element-By-Element Comparison Of Ranbaxy's Tablets In Their Intended Use With Claims 1-6 Confirms Infringement

101. Roche's expert Dr. Henck's comparison of the asserted '953 patent claims 1-6 confirms that Ranbaxy's tablets meet each and every element of each claim and will infringe in their normal intended use by organ transplant and AIDS patients. Henck Tr. III 46:4-56:20; PTX-705.

102. There are no differences between Ranbaxy's valganciclovir hydrochloride tablets and the asserted claims of the '953 patent. Further, any difference that Ranbaxy may assert exists between its tablets and the asserted claims would be insubstantial because Ranbaxy's tablets perform substantially the same function, in substantially the same way, to achieve substantially the same results as the claimed inventions of the '953 patent. Henck Tr. III 58:6-12.

B. Ranbaxy Has The Requisite Intent To Make It Liable Under 35 U.S.C. §271(b) For Inducing Patients' Infringement

1. Ranbaxy Knows Or Should Know That Its Tablets Will Cause Direct Infringement By The Patients For Whom The Drug Is Prescribed

103. Ranbaxy's manufacture and sale of its valganciclovir hydrochloride tablets will induce infringement of asserted Claims 1-6 of the '953 patent. Henck Tr. III 56:21-58:1. Ranbaxy

knows that its tablets should not have any amount of crystallinity because of the '953 patent. FF 20. Nonetheless, Ranbaxy deliberately first manufactures its valganciclovir hydrochloride in crystalline form before spray drying to take advantage of the benefits of making the API in crystalline form as taught by Roche's '953 patent. FF 19. Ranbaxy then subjects its API to a spray-drying process in a crude attempt to avoid Roche's '953 patent, but Ranbaxy knows that its spray-drying process is not fully effective. FF 20. Ranbaxy's Standard Test Procedure allows the release of a crystalline seed of valganciclovir hydrochloride in its tablets up to 0.5% that promotes the substantial conversion of the API to crystalline form when exposed to moisture (FF 21-22, 24-30) and tellingly Ranbaxy never disclosed this procedure to the FDA. R. Singh Tr. V 49:13-52:22; PTX-286 at RVHRX0000966; PTX-383; Chandrashekar Tr. II 7:12-20 (Video Dep. Tr. 129:1-5, 8-22); Chandrashekar Tr. V 120:8-121:10; DX-84; DX-382.

104. Ranbaxy knows that its valganciclovir hydrochloride API is "hygroscopic," meaning that it absorbs moisture from the atmosphere, and that when its valganciclovir hydrochloride absorbs moisture, it converts to crystalline form. FF 31-34. Ranbaxy also knows that the excipients in its finished tablets do not change the hygroscopic nature of the valganciclovir hydrochloride API or impede its conversion to crystalline form, and that the coating on its tablets serves only the aesthetic purpose of mimicking Roche's Valcyte. FF 35-36.

105. Ranbaxy knows by reason of the testimony of Roche's experts Drs. Snydman (PTX-631) and Drew (PTX-449), a Registered Nurse Mr. Marangio (PTX-590) and a pharmacist Mr. Wong (PTX-659) that AIDS and organ transplant patients would store Ranbaxy's tablets in medical pill tray organizers (FF 56-58) and by reason of Dr. Henck's tests that the vast majority of the valganciclovir hydrochloride in Ranbaxy's tablets converts to crystalline form within 24 to 48 hours of being placed in a pill tray (FF 59-65). Ranbaxy also knows by reason of Dr. Henck's

SGF study that at least a majority of the valganciclovir hydrochloride in Ranbaxy's tablets converts to infringing crystalline form within seconds after the tablets are swallowed and that its proposed product label instructs that its tablets are for "oral administration." FF 66-73.

106. Ranbaxy has not relied upon and produced an exculpatory opinion of counsel with respect to the '953 patent demonstrating a good faith belief that conversion of the valganciclovir hydrochloride API in its tablets to crystalline form after its tablets are placed in a medical pill tray organizer or after they are swallowed by a patient does not constitute infringement. Moreover, despite knowing of Roche's infringement contention, Ranbaxy does not intend to change its tablet formulation (FF 36).

2. The Excuses Ranbaxy Offers In Its Attempt To Avoid Inducement Liability Are Nothing More Than Putting Its Head In The Sand

a. Ranbaxy's Professed Ignorance Of The Patients That Will Use Its Tablets And How They Will Be Stored Is Not Credible

107. Dr. Romi Singh, Ranbaxy's Associate Director of the Product Development Group and the Group Leader that developed Ranbaxy's valganciclovir hydrochloride tablets, remarkably feigned ignorance as to the types of patients in the United States who would be administered Ranbaxy's valganciclovir hydrochloride tablets (R. Singh Tr. V 23:8-24:6) and claimed to have never seen a medical pill tray organizer until July 2007 at a Walmart, after the present case had been filed (R. Singh Tr. IV 125:20-126:4).

b. Ranbaxy's Stability Studies Are Under Investigation By The DOJ And FDA

108. Ranbaxy incredibly relies on stability studies carried out at its Paonta Sahib facility, which are unreliable and under criminal investigation by the DOJ and FDA, to support its assertion that the allegedly amorphous valganciclovir hydrochloride in its tablets is stable. The FDA observed that the Paonta Sahib facility "failed to establish and follow an adequate written

stability testing program," and listed multiple problems with Ranbaxy's stability program. Chandrashekar Tr. V 149:14-151:7.

109. Ranbaxy has acknowledged those deficiencies in connection with the very ANDA at issue in this case, ANDA 78-078. Chandrashekar Tr. V 152:2-18; PTX-733. Ranbaxy admitted that "inconsistent entries on Stability Reports" were submitted to the FDA in its ANDA 78-078 based on, inter alia, a practice of inconsistent dating. PTX-733 at RVHRX0041730-31. Further, the Department of Justice (DOJ) is conducting a criminal investigation of Ranbaxy, in which the "Specific allegations under investigation include fabricating bioequivalence and stability data" to support ANDAs. Chandrashekar Tr. V 152:19-153:19.

110. Finally, in September 2008, the FDA issued a warning letter prohibiting the importation of products originating from Ranbaxy's Paonta Sahib and Dewas facilities. Chandrashekar Tr. V 153:24-154:5. The FDA has continued to recommend not approving any new applications listing the Paonta Sahib facility as the manufacturing location for finished pharmaceutical drug products, including Ranbaxy's ANDA 78-078. Chandrashekar Tr. V 154:6-155:16.

c. Ranbaxy's "Dispense In Tight Containers" Argument Is Meritless

111. Ranbaxy's assertion that its tablets would be kept in its HDPE bottles containing molecular sieves until taken by patients is unsupported by the record. There is nothing in Ranbaxy's package insert in its ANDA to require that its tablets be kept in its HDPE bottles. Henck Tr. II 119:9-12. The statement on Ranbaxy's label, "Dispense in tight containers as defined in the USP/NF," is directed to pharmacists, and assumes that pharmacists will take the tablets out of Ranbaxy's original containers and put them into a different container. R. Singh Tr. V 13:5-19. Further, the label on its face allows the pharmacist to dispense Ranbaxy's tablets in

containers that let in at least 10 times as much moisture as Ranbaxy's original containers. R. Singh Tr. V 16:18-18:13; DX-47 at RVHRX0001375.

112. The language "dispense in tight containers" does not tell patients how they should store their valganciclovir tablets. R. Singh Tr. V 18:20-23; 20:9-14; DX-41 at RVHRX0000065. This is apparent because the exact same language appears on the bottle label for Roche's Valcyte tablets (R. Singh Tr. V 19:2-25; PTX-717; PTX-751), and patients routinely store Valcyte in pill trays (FF 56-58; R. Singh Tr. V 20:9-14).

VI. RANBAXY HAS NOT SATISFIED ITS HEAVY BURDEN OF PROVING INVALIDITY UNDER 35 U.S.C. §103 BY CLEAR AND CONVINCING EVIDENCE

A. Advantages Of Oral Prodrug Administration Versus IV Administration

113. Chemical compounds can be effective as drugs if they can be delivered to the body safely and effectively. One method is to inject the drug via the intravenous (IV) route. This introduces the drug immediately into the bloodstream. With IV, 100% of the drug is assumed to be delivered into systemic circulation and the drug is said to be 100% "bioavailable." Stella Tr. X 13:8-14:24. However, this route of administration is very inconvenient and can require the involvement of skilled healthcare personnel. Drew Tr. I 94:23-96:21; Snydman Stip. ¶16. And because IV infusion requires the skin to be punctured, there is always the risk of infections, especially in patients that are immune-compromised. Snydman Stip. ¶15. For this reason, researchers seek ways of delivering drugs orally. Mitscher Tr. IX 58:14-59:1.

B. The Complicated Process Of Prodrug Design

114. One approach used by researchers to overcome the problem of the low oral absorption of a drug molecule is to create a prodrug. Mitscher Tr. IX 50:20-51:10, 58:14-59:1. A prodrug is a new molecular entity which overcomes the barrier through which the parent drug could not pass (such as poor absorption). Stella Tr. X 16:3-17:6; 17:24-18:21; PTX-683. Once the prodrug has

overcome the barrier, the prodrug breaks down, *i.e.* converts back to the parent drug, so the parent drug can exhibit its desired action in the body. Stella Tr. X 18:13-21; Mitscher Tr. IX 50:20-51:10, 124:20-125:1.

115. The process of oral delivery of a prodrug involves the following critical steps. First, the prodrug must dissolve in the gastrointestinal tract (GIT). Stella Tr. X 16:3-15. One cannot predict dissolution behavior of a drug or prodrug in humans based solely on animal models. Mitscher Tr. IX 123:1-20.

116. Second, the prodrug must survive assault by enzymes present in the GIT and on the surface of the cells lining the GIT, whose normal function, amongst other things, is to digest larger molecules (those from food) into smaller ones. Stella Tr. X 16:16-25. This aspect of prodrug discovery and development is nearly impossible to predict. Mitscher Tr. IX 123:1-20; Stella Tr. X 20:23-21:17; PTX-754 at 4.

117. Third, the prodrug must go through the membranes of the cells that line the GIT (the enterocytes) into the bloodstream. Stella Tr. X 17:1-6. When the prodrug is relatively polar (like valganciclovir), it may have to interact with a stereospecific transporter embedded in the enterocytes' cell membranes. Stella Tr. X 21:18-22:2; PTX-754 at 6. This interaction is like a lock and key. Even with the knowledge that a specific key can fit an unknown lock and open the door, one cannot predict whether a different key which has some of the same teeth but also some different teeth could fit the same lock and open the door, because (1) one does not know the shape of the keyhole in the unknown lock, and (2) it is the entire key that must fit the lock and open the door, not just one of the teeth in the key. Thus, even with the knowledge that a prodrug can be stereospecifically transported by an unknown transporter, one cannot predict whether a different prodrug with some of the same chemical groups but also with some different chemical

groups would also be transported by the same transporter, because (1) one does not know the binding site on the unknown transporter, and (2) it is the entire prodrug that must be transported through the transporter, not just the chemical groups which are the same. Stella Tr. X 22:3-24:14; PTX-755 at 3.

118. Fourth, once inside the enterocyte, the prodrug must survive the environment inside, which is designed to break up food products and exogenous materials. One cannot predict, *a priori*, whether this will happen. Stella Tr. X 24:17-25:2; PTX-754 at 9. The fifth step for prodrug delivery is crossing the basolateral membrane of the enterocyte to reach the bloodstream. This is highly unpredictable. Stella Tr. X 25:4-8; PTX-754 at 10. The sixth and final step for prodrug delivery is cleavage of the prodrug to the active parent drug and the prodrug moiety. Stella Tr. X 25:9; PTX-754 at 12. In addition to overcoming the barriers to prodrug delivery, a successful prodrug must also be non-toxic. Stella Tr. X 25:20-26:4, Mitscher Tr. IX 57:11-25, Sloan Tr. IX 27:21-28:2.

119. To discover a prodrug that satisfies all of the foregoing requirements is a difficult task that takes a high degree of creativity. Stella Tr. X 17:24-18:21, 25:10-26:4. There is no way to predict from a chemical structure whether any molecule is going to be a successful prodrug and nontoxic. Stella Tr. X 21:11-17; 23:11-19; 25:4-26:4. This is especially true with respect to nucleoside-analogue prodrugs. Mitscher IX Tr. 51:11-52:1, 55:11-56:19, 57:11-25, 58:9-13, 66:20-69:18, 140:5-13; PTX-682 at 2-6.

120. For example, there must not be phosphorylation of the nucleoside analogue prodrug prior to conversion back to the parent drug because this could create a new and unwanted activated chemical entity that could disrupt the DNA of healthy cells. Mitscher Tr. IX 57:11-25, 58:9-13, 68:8-19, 140:5-13; Gokel Tr. VIII 84:7-9; Sloan Tr. IX 27:21-28:12; DX-171 at R0047110.

121. Phosphorylation can occur at sites having a free (*i.e.*, unblocked) hydroxyl (OH) group. Gokel Tr. VIII 83:22-84:6, 84:10-85:7; Sloan Tr. IX 27:15-20; DX-170 at R0047092. The Beauchamp 1993 paper (DX-171 at R0047110) teaches that phosphorylation sites in nucleoside analogue drugs should be blocked: "it is appropriate when considering prodrugs of other nucleoside analogs to give first priority to chemical derivatives that block the phosphorylation sites." The Beauchamp 1993 paper teaches that a molecule having such an unblocked phosphorylation site can have undesirable toxicity. Mitscher Tr. IX 68:8-19; DX-171 at R0047110.

C. The Novel Mono-ester Prodrug Compounds Of The '953 Patent Claims

122. The compounds of the '953 patent claims are mono-ester nucleoside-analogue prodrugs having an unblocked hydroxyl group. Mitscher Tr. IX 50:11-17, 62:8-11. Chiral centers are locations in a molecule which are asymmetric, meaning that they have a "handedness" or lack of symmetry at that location. The compound of the '953 patent claims has two chiral centers. Because of these chiral centers, the compound exists as a mixture of "diastereomers." Mitscher Tr. IX 129:15-130:4; Gokel Tr. VIII 70:9-71:7, 81:23-83:21; Stella Tr. X 33:20-34:1; PTX-1 at col. 9, lns. 42-53); PTX-688. Diastereomers are compounds that have the property of "handedness" and non-superimposeability. Gokel Tr. VII 129:14-130:1. It is uncommon for diastereomers to be used together in a drug formulation. Mitscher Tr. IX 63:6-22. Normally, only one of the diastereomers is useful and the other diastereomer must be discarded. Mitscher Tr. IX 63:8-17, 64:2-20; Gokel Tr. VII 129:14-130:1. It is also unusual for two diastereomers to crystallize together. Mitscher Tr. IX 86:13-22; 131:12-19; Stella Tr. X 34:2-35:2.

123. It is not uncommon to find that, when a mixture of diastereomers is produced, one or the other diastereomer is toxic or has undesirable pharmacological effects and thus needs to be separated. Mitscher Tr. IX 63:8-17. For example, the antibiotic chloramphenicol is made by

total synthesis which produces a mixture of four diastereomers, but only one of these is antibiotically active and is marketed. The other three forms have to be separated and discarded. Mitscher Tr. IX 64:2-20; PTX-594 at 213.

124. One could not predict whether two diastereomers would have the same physical properties until they were made and tested. Mitscher Tr. IX 63:23-64:1; Gokel Tr. VIII 74:20-24; Sloan Tr. IX 27:5-7. If one decides not to separate diastereomers for use by patients, the FDA approval process becomes more expensive and difficult because one is expected to demonstrate that the presence of the less active diastereomers causes no deleterious effects. Mitscher Tr. IX 63:18-22.

125. Surprisingly, the two diastereomers of valganciclovir, as a mixture, provide superb oral bioavailability for ganciclovir. Stella Tr. X 26:7-24, 27:19-28:18, 30:17-31:3, 34:13-35:2; Sloan Tr. IX 30:9-22; DX-10 at 1148 (Malcolm Declaration at 3). Surprisingly, they crystallize together. Stella Tr. X 34:2-35:2; Mitscher Tr. IX 86:13-22.

126. The compound of the '953 invention satisfies the requirements of a prodrug, and in the words of Dr. Stella, is "a great drug." Stella Tr. X 34:20-35:2. Valganciclovir readily dissolves in the contents of the GI tract, survives the assault from enzymes in the GI tract, passes through the enterocyte cell membranes, and undergoes cleavage to release ganciclovir in the bloodstream. Stella Tr. X 19:25-26:4; PTX-754 at 9, 12.

D. There Are Significant Differences Between The Four Prior Art References Relied Upon By Ranbaxy And The '953 Claimed Subject Matter

1. The Beauchamp '339 Patent Teaches Thousands Of Compounds, None Of Which Are Crystalline Valganciclovir Hydrochloride

127. The Beauchamp '339 patent (DX-101) relates to amino acid esters of nucleoside analogues. The '339 patent does not disclose the mono-valine ester of ganciclovir, *i.e.*, valganciclovir. Mitscher Tr. IX 80:13-23, 115:4-12.

128. Formula I in the '339 patent includes a genus of thousands of compounds. Mitscher Tr. IX 74:18-77:17; PTX-727 at 9. The Examiner's understanding during prosecution of the '953 patent that Formula I of the '339 patent embraces only 16 preferred compounds was incorrect. Dr. Mitscher testified that the number of preferred compounds disclosed in the '339 patent includes around 1600 compounds, and even an order of magnitude higher when the nine salts are taken into account. Mitscher Tr. IX 134:2-8; 138:3-11, 143:6-146:5.

129. The six examples in the '339 patent employ an excess of esterifying agent which does not favor the production of mono-esters (Gokel Tr. VIII 95:20-96:9) and each discloses preparation of bis compounds (Stella Tr. X 64:1-3; DX-101 at Cols. 7-11). While a mono-alaninate ester was produced as a 10% impurity in Example 6 of the '339 patent, it was not a mono-valinate. Mitscher Tr. IX 142:10-19; Gokel Tr. VIII 94:24-95:1. This mono-ester was produced by accident for unknown reasons, and was not a teaching of how to make mono-esters. Mitscher Tr. IX 142:20-23. The '339 patent did not report separately isolating any mono-esters, or testing any mono-ester for oral bioavailability. Mitscher Tr. IX 77:24-78:6; Gokel Tr. VIII 107:6-8; Sloan Tr. IX 28:24-25, 37:22-38:2. Nor did the '339 patent teach a method for making mono-esters. Sloan Tr. IX 29:1-5. Since the '339 patent does not report any mono-ester being isolated or tested (Mitscher Tr. IX 77:24-78:6; Gokel Tr. VIII 107:6-8; Sloan Tr. IX 28:24-25, 37:22-38:2), one skilled in the art would not conclude that any of the improved oral bioavailability reported in the '339 patent was traceable to mono-esters (Stella Tr. X 53:9-19; 56:13-24; 57:7-13; 63:19-64:6; 65:5-15). Thus, the '339 patent provides no motivation to make mono-esters. Mitscher Tr. IX 78:3-9, 78:17-20, 78:25-79:2; DX-101.

130. Formation of a mono-ester is much more difficult than formation of a bis-ester. Mitscher Tr. IX 78:10-12; Gokel Tr. VIII 94:12-15. The '339 patent does not teach how to make mono-

esters or any benefit of selective mono-esterification to prepare mono-esters of ganciclovir (Mitscher Tr. IX 71:18-72:6, 77:21-23, 115:4-12, 142:20-23; Sloan Tr. IX 29:1-5), as opposed to the synthetically easier process of complete esterification to produce bis-esters of ganciclovir (Mitscher Tr. IX 78:10-12; Gokel Tr. VIII 94:12-15).

131. The '339 patent does not disclose that any of the compounds reported therein were in crystalline form. Mitscher Tr. IX 78:21-24. Ranbaxy's expert Dr. Gokel's assertion that the declarants during prosecution of the '953 patent did not adequately try to produce bis-valinate compounds in crystalline form following the Beauchamp '339 patent disclosure is without merit. The declarants made numerous efforts to produce crystalline compounds, including efforts with hydrochloride salts not even attempted in the '339 patent examples. Gokel Tr. VIII 113:1-14; Mitscher Tr. IX 87:25-89:9 (describing attempts by co-inventor Dvorak); DX-8 at 192; Gokel Tr. VIII 48:17-49:2; Maag Tr. X 113:25-114:5, 114:24-115:8 (describing attempts by co-inventor Maag); DX-180 at 6-7; Gokel Tr. VIII 42:19-43:12 (describing attempts by technician Han). Moreover, even Dr. Gokel conceded that one could not know how many attempts would be required to crystallize a compound (Gokel Tr. VIII 119:1-6) and his criticisms of the Dvorak, Maag, and Han Declarations were not based on any experiments that he had done or that were done on his behalf attempting to make ganciclovir bis-valinate acetate or hydrochloride or to repeat the prior art or the work done in the declarations (Gokel Tr. VIII 109:18-111:7).

132. In summary, the teachings in the Beauchamp '339 patent do not render the claims of the '953 patent in suit obvious as Dr. Beauchamp did not attempt to make, isolate, characterize, or ascribe any useful properties to any mono compound in this patent, did not report any bioavailability data for the compounds therein, and did not disclose any compound in crystalline

form. The one mono compound she obtained was an impurity and was not the mono-valine ester. Mitscher Tr. IX 74:4-17; 78:7-79:5.

2. The Beauchamp 1992 Paper Disclosing Blocking Phosphorylation Sites Teaches Away From The '953 Patent Claims

133. The Beauchamp 1992 paper (DX-170) pertains to acyclovir. Mitscher Tr. IX 65:15-66:5. Acyclovir is a different compound from ganciclovir. It does not have the additional hydroxymethyl group present in ganciclovir. Gokel Tr. VIII 77:19-23.

134. The addition of a hydroxymethyl group can make a big difference between molecules. For example, ethylene glycol is an antifreeze, but when a hydroxymethyl group is added, it becomes glycerine, which is a safe food additive. Mitscher Tr. IX 140:19-141:16; PTX-725 at 3.

135. The additional hydroxymethyl group in ganciclovir results in a difference in properties between ganciclovir and acyclovir. For example, ganciclovir is about ten times more toxic than acyclovir. Mitscher Tr. IX 147:13-18. Also, while acyclovir is used to treat herpes simplex, ganciclovir is used to treat cytomegalovirus (CMV) infections. Mitscher Tr. IX 92:3-9. Ganciclovir is much more effective against CMV than acyclovir. Gokel Tr. VIII 78:4-7.

136. The Beauchamp 1992 paper is not about prodrugs of ganciclovir. Mitscher Tr. IX 65:15-66:5, 94:5-23. The compounds in the Beauchamp 1992 paper are single compounds and do not exist as a mixture of diastereomers. Mitscher Tr. IX 66:6-14.

137. The procedures in the Beauchamp 1992 paper, if applied to ganciclovir, would produce bis-esters, not mono-esters. Stella Tr. X 51:20-52:25. The 1992 Beauchamp paper teaches away from producing anything but completely esterified molecules. Mitscher Tr. IX 66:15-67:23; DX-170 at R0047088.

138. The Beauchamp 1992 paper does not teach or suggest the mono-valine ester of ganciclovir, nor does it teach or suggest mono-valine esters of ganciclovir as hydrochloride salts

in crystalline form. Mitscher Tr. IX 72:17-20, 73:23-74:3, 80:13-23; Stella Tr. X 51:20-52:25; Gokel Tr. VIII 77:1-5; 88:9-25, 89:11-21.

139. One always has to be concerned about the toxicity of drug molecules. Sloan Tr. IX 27:21-28:12. The compounds of the Beauchamp 1992 paper do not have free hydroxyl groups. Gokel Tr. VIII 88:9-25, 89:11-21. The Beauchamp 1992 paper taught that blocking the phosphorylation sites is necessary to avoid toxicity due to phosphorylation of unconverted prodrug. Mitscher Tr. IX 66:15-67:23; PTX-682 at 11-13; DX-170 at R0047088. The Beauchamp 1992 paper thus teaches away from the mono-valine ester of ganciclovir, which has a free hydroxy phosphorylation site. Mitscher Tr. IX 66:15-67:23, 69:4-15; PTX-682 at 11-13.

3. The Beauchamp 1993 Paper Is Cumulative To The Phosphorylation Teaching Away

140. The Beauchamp 1993 paper (DX-171) is the only reference cited by Ranbaxy that was not of record during the prosecution of the '953 patent. However, the Beauchamp 1993 paper is a review, *inter alia*, of the work reported in the Beauchamp 1992 paper and cumulative to the papers of record during prosecution of the '953 patent. Gokel Tr. VIII 77:6-12, Gokel Tr. VII 124:9-24. Like the Beauchamp 1992 paper, it relates to esters of acyclovir, not ganciclovir, and includes a statement which teaches away from the mono-valine ester of ganciclovir, which has a free hydroxy phosphorylation site. Mitscher Tr. IX 68:8-19; 73:23-74:3; Gokel Tr. VIII 83:22-84:6, 84:10-85:7; Sloan Tr. IX 27:15-20; DX-171 at R0047110; PTX-682 at 9-13; PTX-688.

4. The Martin Paper (1987) Teaches Away From Making Mono-Esters

141. The Martin paper (DX-154 at 3) describes that production of the mono-form prodrug would result in a reduction in activity: "A reduction in activity is associated with the mono-O-acyl derivative **22**." This was a disincentive to make mono-esters and a teaching away from the '953 invention, which is a mono-ester. Mitscher Tr. IX 79:6-80:12. The Martin paper does not

disclose any amino acid esters and does not disclose valganciclovir hydrochloride. Mitscher Tr. IX 80:13-23; DX-154; Gokel Tr. VIII 77:1-5.

E. The Level Of Ordinary Skill In The Art

142. The level of skill is addressed at FF 11.

F. Ranbaxy Has Not Asserted That Claims 1-6 Of The '953 Patent Are Anticipated By Any Reference And Its Experts Admit That They Are Not

143. Ranbaxy did not assert in the Final Pretrial Order that the prior art anticipates Claim 1-6 of the '953 patent and Claims 1-6 are not anticipated by any prior art reference upon which Ranbaxy relies. The prior art did not disclose: (1) the valganciclovir molecule, *i.e.* the mono-valinate ester of ganciclovir; (2) in the form of a hydrochloride salt; and (3) in crystalline form. Mitscher IX Tr. 49:5-8, 80:13-23. Ranbaxy's expert Dr. Gokel conceded that none of the prior art he was aware of anticipates any claim of the '953 patent. Gokel Tr. VIII 76:12-24. Ranbaxy's expert Dr. Sloan also admitted that no one isolated valganciclovir hydrochloride prior to the time of the invention of the '953 patent. Sloan Tr. IX 27:1-4.

G. The Prior Art Would Not Have Rendered Claims 1-6 Of The '953 Patent Obvious

144. As indicated above, there are numerous differences between each prior art reference and the claimed invention. Even if the references are combined, they do not disclose all of the features of the '953 invention. There was no teaching or suggestion in the prior art of the mono-valine ester diastereomers of ganciclovir, which are never mentioned by name, nor are any properties given for them. In fact, there is no evidence that the mono-valine esters of ganciclovir were ever even made or suggested before the '953 invention. Mitscher Tr. IX 48:15-20; 73:7-75:1; 77:19-80:23. Moreover, one of skill in the art would not have expected that valganciclovir hydrochloride in crystalline form would have provided improved oral bioavailability over ganciclovir. Stella Tr. X 19:25-20:4; 24:5-15.

H. Ranbaxy's Contentions About Obviousness Are Incorrect

145. Ranbaxy's experts Drs. Gokel and Sloan did not address the issue of diastereomers and the ability of the diastereomers to in fact form a crystalline material and to show superb bioavailability. Stella Tr. X 12:3-25. In fact, Dr. Gokel did not mention diastereomers at all in his direct testimony. Gokel Tr. VIII 83:14-21. One of skill in the art would not be able to predict based on valacyclovir whether either or both of the two diastereomers of valganciclovir would also interact with the stereospecific transporter suggested in the Beauchamp 1992 paper. Stella Tr. X 24:5-14; PTX-755 at 3. The superb bioavailability seen with valganciclovir diastereomers was not expected. Stella Tr. X 31:4-10; 34:21-35:2.

146. Ranbaxy's expert Dr. Sloan's assertion to the contrary is a hindsight guess. Sloan Tr. IX 24:13-25. Dr. Sloan relied upon comments by the Examiner during prosecution of the '953 patent (Sloan Tr. IX 19:10-25), but the Examiner did not consider that the results obtained for the mono-valinate were much better than the bis-valinate, and never said there were no unexpected results for the mono-valinate as compared to the bis-valinate (Stella Tr. X 26:7-24, 28:18-21, 32:9-33:19). The greater than 50% bioavailability achieved by valganciclovir, an 8-fold factor increase over ganciclovir, was quite outstanding and would not be expected. Stella Tr. X 31:4-10; 34:21-35:2. Even Ranbaxy's expert Dr. Sloan admitted that it was a bonus for valganciclovir hydrochloride to improve oral bioavailability to above 40%. Sloan Tr. IX 31:14-32:11.

147. In her '339 patent, Dr. Beauchamp followed her own advice expressed in her 1992 and 1993 papers and did not leave a free hydroxyl group capable of phosphorylation. Mitscher Tr. IX 71:18-72:14. The three Beauchamp references relied upon by Ranbaxy's experts did not teach or suggest making the mono-valine esters of ganciclovir, let alone making a mixture of mono-valine ester diastereomers of ganciclovir as hydrochloride salts in crystalline form. Mitscher Tr. IX 80:13-23; Stella Tr. X 51:20-52:25.

148. Ranbaxy's experts Drs. Gokel and Sloan trivialized the prodrug discovery process. Their analysis was basically a hindsight analysis. Stella Tr. X 12:3-25. Indeed, Ranbaxy's expert Dr. Gokel had never worked in the area of prodrugs at the time of his deposition in this case. Gokel Tr. VIII 108:13-109:13. Ranbaxy's other expert Dr. Sloan has not worked with oral prodrugs for at least the last 10 years. Sloan Tr. IX 29:10-12. Dr. Sloan was not familiar with the bis-valinate esters of ganciclovir prior to the time this litigation began. Sloan Tr. IX 29:6-9.

I. There Is Compelling Objective Evidence Of Nonobviousness

1. Valcyte Satisfied A Long-Felt But Unsatisfied Need

149. Anti-CMV drugs prior to Valcyte had serious disadvantages. Drew Tr. I 90:7-8, 91:19-93:7, 93:14-96:21, 97:6-99:8, 100:14-101:17, 104:12-22; Snydman Stip ¶11-17. Valcyte satisfied a long felt but unsatisfied need for a drug with the anti-CMV efficacy of IV ganciclovir and the safety and convenience of oral dosing. Drew Tr. I 102:16-103:14; 106:18-107:18; 110:9-111:12; Lesser Tr. I 60:9-62:23; Snydman Stip. ¶19; PTX-114; PTX-458; PTX-639 at 21; PTX-647 at 611-12.

2. Valcyte Has Been A Great Commercial Success

150. Valcyte has been a tremendous commercial success. Grabowski Tr. IX 155:15-20, 156:2-9, 157:6-158:25, 159:21-160:7, 161:19-20, 163:1-5; 165:12-19; Lesser Tr. I 53:14-15; PTX-548; PTX-549; PTX-551; PTX-552.

151. The commercial success of Valcyte is attributable to the medical benefits of its active ingredient, not marketing or other factors. Drew Tr. I 112:15-23; Snydman Stip. ¶24; Grabowski Tr. IX 160:8-16, 164:21-165:7, 166:16-167:2, 170:1-171:4, 171:12-19; PTX-258. Ranbaxy's expert Mr. Tate's assertions that Valcyte's commercial success is attributable to marketing, an increased length of therapy and/or an overall growth in the number of solid organ transplants are contrary to the record. Drew Tr. I 114:21-115:4, 116:13-117:10, 118:2-14; Snydman Stip. ¶¶25-

27; Lesser Tr. I 76:17-77:8; Grabowski Tr. IX 162:15-23, 168:1-19, 168:25-169:16; Tate Tr. VIII 160:15-162:17, 164:19-167:6; PTX-553; PTX-563.

3. Valcyte Provides Unexpectedly Superior Results

152. Several properties of Valcyte are both highly beneficial and highly unexpected. FF 125, 146.

VII. RANBAXY HAS NOT SATISFIED ITS HEAVY BURDEN OF PROVING THAT THE '953 PATENT CLAIMS ARE INVALID UNDER 35 U.S.C. §112 ¶1 FOR FAILING TO SATISFY THE WRITTEN DESCRIPTION REQUIREMENT

153. A person skilled in the art would understand the words "in crystalline form" in '953 Claim 1 mean that crystallinity in the context of the patent should be determined by employing a standard and reliable analytical test, *i.e.*, XRD. Henck Tr. II 104:23-105:3; FF 8.

154. The prosecution history of the '953 patent confirms that the presence of valganciclovir hydrochloride in crystalline form should be detected by XRD. In declarations submitted to the PTO during prosecution, inventors Dvorak and Maag and technician Han each referred to testing valganciclovir hydrochloride and other materials for crystallinity by XRD. Gokel Tr. VIII 119:19-22, DX-178 at 7; DX-180 at 5; DX-183 at 3; Henck Tr. II 107:6-15.

155. The patent specification as filed in 1994, including its description of the structure of valganciclovir hydrochloride and the methods for synthesizing it and preparing it in crystalline form, would have clearly conveyed to a person skilled in the art that the inventors were "in possession" of valganciclovir hydrochloride in crystalline form and that crystalline valganciclovir hydrochloride was readily confirmable by XRD which was the standard technique for detecting crystallinity at that time. FF 8. In 1994, as now, the typical medicinal chemist or drug formulator would not have had the equipment and expertise to conduct XRD analyses for him- or herself. Rather, the standard practice in 1994 was for the medicinal chemist or drug formulator to send a sample of the material in question to a co-worker with the requisite

expertise and equipment for XRD. Such individuals were commonly present in the analytical chemistry departments of research-based pharmaceutical companies. Henck Tr. II 102:7-103:2; Mitscher Tr. IX 60:2-16.

156. This is exactly what the '953 patent inventors did. Henck Tr. II 103:3-9. For example, Charles Dvorak, an inventor of the '953 patent, sent samples to members of Roche's pharmaceutical analytical department to be analyzed by XRD. Since Mr. Dvorak was not a crystallographer and did not have experience with interpreting XRD analyses, he relied on his colleagues in that department to perform the XRD analyses, interpret and provide him with the results. Dvorak Video Dep. Tr. 163:6-164:20, 188:6-189:4, 223:14-224:7, 226:11-227:12, 397:18-399:1, 400:15-23, 458:4-459:7. This is also exactly what Ranbaxy's scientists do -- they send samples of valganciclovir hydrochloride to Ranbaxy's analytical department to determine whether the samples contain crystalline material. Khanduri Tr. IV 15:20-16:13, 30:15-25.

157. The inventors requested and received the results of XRD tests to detect valganciclovir hydrochloride in crystalline form before the filing date of the '953 patent application. Co-inventor Paul Fatheree's notebook 18951, page 142, sample 60, describes the first preparation of valganciclovir hydrochloride on June 2, 1994, and the analysis of that material by XRD on June 10, 1994. The '953 patent, Example 3, discloses a similar experiment on a larger scale. Maag Tr. X 74:18-81:23; PTX-1 at Cols. 23-24; PTX-255A; PTX-255B; PTX-255C.

158. Ranbaxy presented no evidence at trial in support of its assertions that the '953 patent claims are invalid for lack of patentable subject matter under 35 U.S.C. §101 and invalid for indefiniteness under 35 U.S.C. §112 ¶2.

PART II: CONCLUSIONS OF LAW

I. CLAIM CONSTRUCTION

1. The words of a claim are generally given the "ordinary and customary meaning" they "would have to a person of ordinary skill in the art in question . . . as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). The person of ordinary skill is deemed to read the claim in light of the "intrinsic evidence" of the patent, *viz.*, the claim language itself, the patent specification and the patent's prosecution history. *Id.* Courts are also free to consult sources that are extrinsic to the patent, *e.g.*, dictionaries and expert testimony, as long as they do not contradict the intrinsic evidence. *Id.* at 1317-18. Claim construction is a question of law. *Markman v. Westview Instruments*, 517 U.S. 370, 372 (1996).

2. Claims 1 and 2 of the '953 patent are "product" claims (also called "composition of matter" claims). Such claims define the claimed subject matter solely in terms of its structure or other physical characteristics. They cover a given product, *e.g.*, a chemical compound or a pharmaceutical composition, regardless of *how* the product is made,[2] regardless of *when* the product is made,[3] regardless of whether the product is mixed with other materials,[4] and

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[2] *AFG Indus. v. Cardinal IG Co.*, 375 F.3d 1367, 1372-73 (Fed. Cir. 2004) (rejecting argument that claimed product had to be made by the process described in the patent because that construction "would impermissibly import a process limitation into a pure product claim"); *Exxon Chem. Patents Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1557 n.4 (Fed. Cir. 1995) (rejecting construction that would have limited claim to composition made by particular process because such construction would be "at odds with the doctrine that a product claim is infringed by any product containing every claim limitation, regardless of how the product is made").

[3] *Zenith Labs. v. Bristol-Myers Squibb Co.,* 19 F.3d 1418, 1421-22 (Fed. Cir. 1994) (claim reciting crystalline form of antibiotic compound covered that product when it was momentarily formed in the patient's stomach after ingestion, even though pills in the form in which they were sold by defendant did not satisfy the claim); *Exxon*, 64 F.3d at 1558 (A product claim "is entitled to a broad[ ] scope that is not time-limited, one that reads on any product at any time that contains the claimed proportions of ingredients.").

[4] *Glaxo, Inc. v. Novopharm Ltd.*, 110 F.3d 1562, 1565-66 (Fed. Cir. 1997) (claim directed to "crystalline form 2" of drug not limited to pure form 2, but also covered mixtures of form 2 and a different crystalline form); *SmithKline Beecham Corp. v. Apotex Corp.,* 403 F.3d 1331, 1339-41 (cont'd)

regardless of whether the product provides any of the advantages that may be described in the specification or prosecution history.[5]

3. There is no dispute that the language in Claim 1 of the '953, "The compound 2-(2-amino-l,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-l-propanyl-L-valinate hydrochloride", is valganciclovir hydrochloride. The remaining language "in crystalline form" means that the valganciclovir hydrochloride molecules are arranged in a regularly repeating three dimensional pattern of molecules. FF 6. Claim 1 of the '953 patent is therefore properly construed as covering valganciclovir hydrochloride in crystalline form, *i.e.*, in a regularly repeating three-dimensional pattern of molecules - nothing more and nothing less.

4. Ranbaxy attempts to avoid a finding of infringement by reading three extraneous limitations into claim 1: Ranbaxy argues that the claim: (1) should be limited to material that is substantially all crystalline when made; (2) excludes crystalline material that results from the conversion of amorphous material; and (3) should be construed as requiring the presence of a multi-peak XRD "fingerprint" that it alleges is characteristic of valganciclovir hydrochloride in crystalline form.

5. Ranbaxy's attempt to read the first two of these extraneous limitations into the claims is based on statements in the patent specification that describe how the use of the crystalline form

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(Fed. Cir. 2005) (claim directed to "Crystalline paroxetine hemihydrate" covered composition that included only a small amount of the crystalline compound formed as an unwanted contaminant by a conversion process, with the bulk of the composition being the unpatented amorphous form).

[5] *SmithKline,* 403 F.3d at 1339 (rejecting attempt to read pharmaceutical and commercial properties into claim reciting chemical compound: "A description of [advantageous commercial] characteristics does not redefine a compound with an established and unambiguous structural definition."); *Zenith*, 19 F.3d at 1421 (product claim reciting "Crystalline cefadroxil monohydrate" covered that compound formed by conversion in patient's stomach, even though prosecution was "replete with arguments" that the importance of the invention was the discovery of a way to manufacture the compound).

of a given compound, rather than the amorphous form, is advantageous in the manufacturing of pharmaceutical products. But claim 1 is directed to a chemical compound *per se,* not a method of manufacturing such a compound. Thus, it makes no difference that the accused crystalline valganciclovir hydrochloride forms by conversion of material that starts out in amorphous form and disposes of Ranbaxy's assertion that the claim is limited to compositions containing substantially pure crystalline material. FF 13-16.

6. Ranbaxy puts great weight on a statement by applicants during prosecution that conversion of a drug from amorphous to crystalline form is "catastrophic" to the quality of an oral dosage form. But this statement is just another assertion of a benefit of manufacturing and storing a crystalline product over an amorphous product, *i.e.*, that the crystalline form is stable while the amorphous form is not. The evidence at trial showed that this statement was correct: the supposedly amorphous API in Ranbaxy's product converts to crystalline form and the tablets crack upon exposure to normal indoor conditions. FF 65. However, Roche does not allege that the amorphous material infringes. Only the crystalline valganciclovir hydrochloride that results from the conversion of the amorphous material is accused of infringement. The statement that conversion from amorphous to crystalline form is catastrophic to the quality of an oral dosage form provides no basis to carve out from the scope of product claim 1 crystalline material that is formed by way of such conversion. Further, Roche never distinguished the claims over the prior art on this ground.

7. Finally, Ranbaxy's attempt to read a "fingerprint" limitation into claim 1 must be rejected because there is no such fingerprint recited in the claim, nor is such a fingerprint described in the specification or prosecution history. It might be different if claim 1 was attempting to claim a specific crystalline form over another and recited a number of specific XRD peaks. For

example, the claim in *Zenith* recited 37 specific peaks, and the failure to prove that all 37 were present when the accused compound converted to crystalline form ultimately led to a finding of noninfringement. 19 F.3d at 1423-24. But Claim 1 claims crystalline valganciclovir hydrochloride *per se* and not one specific form over another, and thus, this kind of fingerprint limitation is absent from claim 1, and it would be an error of law to construe the claim as containing it.[6]

8. Dependent claim 2 of the '953 patent reads: "An antiviral pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable excipient." When claim 2 recites "the compound of claim 1," it is referring to valganciclovir hydrochloride in crystalline form, the meaning of which was discussed above. There is no dispute that an "excipient" is a "substance[] other than the active ingredient that. . . [can be] added to the formulation in manufacturing the drug." *Warner-Lambert Co. v. Teva Pharms. USA*, 418 F.3d 1326, 1330 n.1 (Fed. Cir. 2005). "'Pharmaceutically acceptable' means generally safe and non-toxic and . . . acceptable for . . . human pharmaceutical use." PTX-1 at Col. 10 Lns. 1-4. The word "comprising" is a term of art which means that the claim does not exclude additional, unrecited elements.[7] Accordingly, claim 2 requires the presence of valganciclovir hydrochloride in crystalline form and a pharmaceutically acceptable excipient, but does not exclude the presence of other materials, such as amorphous valganciclovir hydrochloride.

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[6] *E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430, 1433 (Fed. Cir. 1988) ("[W]e know of no principle of law which would authorize us to read into a claim an element which is not present. . . . The difficulty is that, if once we begin to include elements not mentioned in the claim ... we should never know where to stop.") (*quoting McCarty v. Lehigh Valley R. Co.*, 160 U.S. 110, 116 (1895)).

[7] *Vivid Techs. Inc. v. Am. Sci. & Eng'g, Inc*. 200 F.3d 795, 811 (Fed. Cir. 1999) ("'comprising' implements the general rule that. . .infringement is not avoided by the presence of elements or steps in addition to those specifically recited in the claim.").

9. Dependent claims 3, 4, 5, and 6 of the '953 patent are directed to methods of treating an "animal" infected with a virus by administering a therapeutically effective amount of "the compound of claim 1," *i.e.*, valganciclovir hydrochloride in crystalline form. The term "animal" in claim 3 includes humans. PTX-1 at Col. 10 Lns. 63-65. The other terms in claims 3-6 do not require separate analysis. In claim 4, the reference to "the method of claim 2" is an obvious typographical error. FF 18. The Court can and should correct this typographical error.[8]

II. INFRINGEMENT

A. Infringement Generally/Burden Of Proof

10. To show infringement, the plaintiff must establish that the accused product includes each limitation of a claim or an equivalent of each limitation. *Warner-Lambert Co. v. Teva Pharms. USA*, 418 F.3d 1326, 1340 (Fed. Cir. 2005). Infringement is an issue of fact, *id*., which must be proven by a preponderance of the evidence, *id*. at 1341 n.15. Although most patents contain several claims, a party need only infringe one of them to be liable for infringement. *Bio-Technology General Corp. v. Genentech, Inc.*, 80 F.3d 1553, 1562 n.8 (Fed. Cir. 1996).

11. The present case was brought under 35 U.S.C. §271(e)(2). That statute allows a patentee to sue for infringement even though the generic drug is not on the market and infringement in the traditional sense has not yet occurred. Instead, the court must perform a "traditional infringement analysis" as to the product the generic company will market after the ANDA is approved. *Allergan Inc. v. Alcon Labs.*, 324 F.3d 1322, 1331 (Fed. Cir. 2003). The future infringement that a patentee can rely on in a §271(e)(2) case includes both direct infringement under §271(a) and inducement of infringement under §271(b). *Id.*

[8] *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1331 (Fed. Cir. 2005) (district court erred when it held that it lacked authority to correct an obvious error in the dependency of a claim because "[w]hen a harmless error in a patent is not subject to reasonable debate, it can be corrected by the court, as for other legal documents").

B. Inducement Of Infringement Under 35 U.S.C. §271(b)

12. A party who makes, uses, offers for sale, or sells a patented invention is liable as a "direct" infringer under 35 U.S.C. §271(a). A party who does not directly infringe a patent may nonetheless be liable for inducing infringement by another. *See* 35 U.S.C. §271(b) ("Whoever actively induces infringement of a patent shall be liable as an infringer.") To establish inducement liability, the plaintiff must show: (1) direct infringement by the party allegedly induced to infringe (here, the patients); and (2) that the accused inducer (here, Ranbaxy) had the requisite intent. *Broadcom Corp. v. Qualcomm Inc.*, 543 F.3d 683, 697 (Fed. Cir. 2008).

13. Intent to induce infringement need not be proven by direct evidence. Rather, "this intent may be established through circumstantial evidence," and "may be inferred from all of the circumstances." *Broadcom*, 543 F.3d at 699. The intent element is satisfied by showing that the defendant "knew or should have known his actions would induce actual infringements." *Id.*; *accord DSU Medical Corp. v. JMS Co.*, 471 F.3d 1293, 1304 (Fed. Cir. 2006) (*en banc*).

14. Although inducement requires intent to "encourage" another's infringement, there is no requirement for the inducing party to actually communicate such encouragement to the party being induced to directly infringe. *Ricoh Co. v. Quanta Computer Inc.*, 2008 U.S. App. LEXIS 25850, *45-46 (Fed. Cir. Dec. 23, 2008). To the contrary, circumstantial evidence showing that the defendant knows of the patent and knows or should know that its actions will induce actual infringement is all that is required. *Id.* at *47-48.

15. Because a competent opinion of counsel is relevant to whether the defendant "knew or should have known" that its actions would cause another to infringe, the failure to procure such an exculpatory opinion – as Ranbaxy failed to do in this case – constitutes circumstantial evidence of intent to induce infringement. *Broadcom*, 543 F.3d at 699.

16. The Federal Circuit has approved findings of inducement liability under circumstances very similar to those presented in this action.[9] Post-*DSU* decisions by district courts have also found inducement liability under circumstances similar to those presented here.[10]

C. Ranbaxy's Arguments That It Will Not Be Liable For Inducing Infringement Of The '953 Patent Are Meritless

17. Citing *Warner-Lambert Co. v. Apotex Corp*., 316 F.3d 1348 (Fed. Cir. 2003), and *Allergan, Inc. v. Alcon Labs*., 324 F.3d 1322 (Fed. Cir. 2003), Ranbaxy argues that "mere knowledge" that patients using its product will infringe the '953 patent is not enough to make it liable for inducing that infringement. But the facts here are entirely different from *Warner-Lambert* and *Allergan*. The ANDAs in those cases sought approval to market drugs only for uses that were *not* covered by the asserted patents. Thus, infringement would have occurred only if the products were used in a manner *contrary* to the manufacturers' instructions. Further, the court refused to draw inferences that the products would be used for purposes for which there was no FDA approval. *Warner-Lambert*, 316 F.3d at 1364-65.

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[9] *Broadcom*, 543 F.3d at 700 (district court properly inferred intent to induce infringement where defendant was on notice of patentee's infringement contentions, failed to change product or to instruct its customers to use it in way that would avoid infringement, and failed to produce opinion of counsel that it was not infringing or inducing infringement); *Zenith*, 19 F.3d at 1421-22 (claim reciting a crystalline form of a drug was properly construed to read on that product when it was momentarily formed in the patient's stomach after ingestion, and the defendant generic drug company would have been liable under §271(b) for inducing the patients' infringement if adequate evidence of conversion had been presented).

[10] *Wing Shing Prods. v. Simatelex Manufactory Co*., 479 F. Supp. 2d 388, 408 (S.D.N.Y. 2007) (foreign manufacturer liable for inducing infringement because it "knew or should have known that (1) the goods it was manufacturing infringed on [plaintiff's] patent and (2) the goods were headed for the United States."); *Fellowes Inc. v. Michelin Prosperity Co*., 491 F. Supp. 2d 571, 589-590 (E.D. Va. 2007) (foreign defendants' designing and manufacturing the accused products, which they knew or should have known infringed the asserted patents, coupled with their solicitation of U.S. retailers to sell them, made them liable for inducing the retailers' infringement).

18. Here, there is no need for inferences. Ranbaxy is seeking FDA approval to market its product for the prevention of CMV disease in organ transplant patients and the treatment of CMV retinitis in AIDS patients – uses explicitly covered by the '953 patent's method claims. FF 5. Product claims 1 and 2 contain no method of use limitations at all. Thus, the '953 patent will be infringed when Ranbaxy's product is used in the normal manner for the very same indications for which Ranbaxy is seeking approval.

19. Ranbaxy argues that because it does not instruct patients to use pill trays, it does not "encourage" the patients to infringe and therefore is not liable for inducing their infringement. This argument has no applicability to the infringement that occurs when patients swallow Ranbaxy's tablets, since Ranbaxy expressly instructs that the tablets be taken orally. FF 66. Even with respect to the infringement that occurs when the tablets are stored in medical pill tray organizers, Ranbaxy is incorrect. The statement that an inducer must "encourage" another's infringement is just another way of stating the statutory requirement that inducement must be "active." 35 U.S.C. §271(b) ("Whoever *actively* induces infringement . . . shall be liable as an infringer.") (emphasis added). The Federal Circuit has interpreted this concept broadly:

> "Actively inducing," like "facilitating," requires an affirmative act of some kind: Of course inducement has connotations of active steps knowingly taken—knowingly at least in the sense of purposeful, intentional as distinguished from accidental or . inadvertent. But with that qualifying approach, the term is as broad as the range of actions by which one in fact causes, or urges, or encourages, or aids another to infringe a patent.

Tegal Corp. v. Tokyo Electron Co., 248 F.3d 1376, 1378-79 (Fed. Cir. 2001). Further, the Federal Circuit has expressly rejected the notion that the "encouragement" necessary for inducement liability must be communicated to the party being induced to infringe. *Ricoh*, 2008 U.S. App. LEXIS 25850, *45-46.

20. Ranbaxy's ostrich-like assertion that it can ignore the evidence of conversion provided to it in the course of this lawsuit is indefensible.[11]

D. Ranbaxy's Criticisms Of The Work Of Roche's Expert Dr. Henck Are Meritless

21. In reviewing the evidence on the issue of infringement, the Court should take into consideration that Ranbaxy's experts merely criticized Dr. Henck's methodology, but performed no tests of their own. FF 74-75.[12] Dr. Henck's conclusions are entitled to added weight because he relied on Ranbaxy's own internal test procedure for detecting the presence of valganciclovir hydrochloride in crystalline form. FF 41, 44-46, 96.[13] Moreover, all three of Dr. Henck's studies, *viz*., the medical pill tray organizer study, the SGF study, and the crystalline seed study, were shown to be reliable, and Ranbaxy's criticisms thereof were shown to be meritless. FF 77-100.[14]

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[11] *Qualcomm*, 543 F.3d at 700 (affirming finding of inducement where accused party was on notice of the asserted patents and patent holder's infringement contentions but failed to give its customers instructions on how to avoid infringement after lawsuit was filed, and also failed to modify its products so that they would not infringe when used by customers); *Fellowes*, 2007 U.S. Dist. LEXIS 45545, *46 (inducement found where defendants were made aware of patent when suit filed, and thereafter knew or should have known that the retailers' actions would constitute infringement); *Wing Shing*, 2007 U.S. Dist. LEXIS 25284, *52 (inducement found where, after being made aware of patent by the filing of suit, defendant knew or should have known that sales made thereafter would result in infringement).

[12] *See Electro Med. Sys. v. Cooper Life Sciences, Inc.*, 34 F.3d 1048, 1055 (Fed. Cir. 1994) (approving district court's ruling in favor of patentee who conducted experiments to show infringement where defendant performed no tests to rebut the findings of the patentee's expert but instead offered a "plethora of opinion testimony unsupported by any backup evidence").

[13] *See NCube Corp. v. Seachange Int'l, Inc.*, 436 F.3d 1317, 1323 (Fed. Cir. 2006) (finding of infringement affirmed where patentee's expert "supported his opinion by relying on [the defendant's] own technical documents").

[14] With regard to Ranbaxy's criticism of Dr. Henck's crystalline seed study, it is well-accepted that "[a]n expert witness is permitted to use assistants in formulating his expert opinion." *Dura Auto Sys. of Ind., Inc. v. CTS Corp.*, 285 F.3d 609, 612-13 (7th Cir. 2002); *see also Titan Stone, Tile & Masonry, Inc. v. Hunt Constr. Group, Inc.*, 2007 WL 1659056, at *3-4 (D.N.J. June 5, 2007) (*quoting Dura* while rejecting a motion in limine to preclude expert opinion based upon (cont'd)

III. VALIDITY

A. The Presumption Of Validity/Burden Of Proof

22. "Issued patents have a strong presumption of validity in infringement proceedings." *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999) (*citing* 35 U.S.C. §282). A party challenging the validity of any claim has the heavy burden of proving invalidity by "clear and convincing" evidence. *Id.* "[T]he challenger's burden is especially difficult when the prior art. . . was before the PTO examiner during prosecution of the application." *Id. See also Metabolite Labs. Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1368 (Fed. Cir. 2004) ("where the PTO previously considered the prior art reference, [there is] an even heavier burden to prove invalidity"). This extra-heavy burden applies also where one of the references being relied upon to show invalidity was not cited during prosecution, but is cumulative to other references that were of record. *Id.*

B. Ranbaxy Has Waived Any Assertion That The '953 Patent Claims Are Invalid Under 35 U.S.C. §102

23. Ranbaxy failed to set forth in the Final Pretrial Order any defense that the subject matter claimed by the '953 patent is unpatentable for anticipation based on any of the subsections of 35 U.S.C. §102. FF 143. Accordingly, Ranbaxy has waived the right to assert invalidity under section 102. *Phoenix Canada Oil Co. v. Texaco, Inc.*, 842 F.2d 1466, 1476 (3d Cir. 1988).

C. Obviousness Under 35 U.S.C. §103

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data extracted by expert's assistant). As Federal Rule of Evidence 703 makes clear: "The facts or data in the particular case upon which an expert bases an opinion or inference may be those perceived by *or made known* to the expert. . . ." This conclusion is even more certain when the technicians do not exercise expert-level judgment but instead are mere "data gatherers." *Dura Auto*, 285 F.3d at 613. In this case it is uncontested that the technicians in Dr. Henck's laboratory at SSCI merely followed Ranbaxy's Standard Test Procedure to gather the data for Dr. Henck's opinions. FF 24-25.

1. The Factors That Must Be Considered In Evaluating Obviousness

24. Obviousness under 35 U.S.C. §103 is a legal issue based on four underlying factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *See*, *e.g.*, *Eli Lilly and Co. v. Zenith Goldline Pharms.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006). For a chemical compound, a *prima face* case of obviousness requires: (1) structural similarity between the claimed compound and the prior art; (2) motivation to modify the prior art compound(s) to arrive at the claimed molecule; and (3) a reasonable expectation that the new compound will be effective for its intended purpose. *Eli Lilly*, 471 F.3d at 1377. The Court should also consider the unique *properties* of the claimed compound. *Id*. at 1378.

25. 35 U.S.C. §103 requires analysis of a claimed invention *as a whole*. It is error to consider the obviousness of individual claim limitations in isolation.[15]

2. The Supreme Court's 2007 KSR Decision

26. The Supreme Court recently relaxed the standard for evaluating obviousness in cases where the prior art provided "a finite number of identified, predictable solutions" to the problem the inventor was trying to solve. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007). *KSR* involved the obviousness of a patented gas pedal for automobiles that combined the features of a prior art adjustable acceleration pedal with a prior art sensor for detecting an acceleration pedal's position. *Id*. at 1734. The Federal Circuit has distinguished *KSR*, in which the prior art provided "a finite number of identified, predictable solutions," from the facts presented in cases

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[15] *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004) ("The 'as a whole' instruction in title 35 prevents evaluation of the invention part by part."); *Gillette Co. v. S.C. Johnson & Son*, 919 F.2d 720, 724 (Fed. Cir. 1990) (trial court erred by focusing on obviousness of individual limitations rather than combination of all limitations as a whole).

involving pharmaceutical compounds, noting that the design of a new drug involves a large number of steps and choices, the results of which are unpredictable.[16]

3. "Obvious To Try" Is Not The Standard

27. Claimed subject matter is not unpatentable under §103 merely because it would have been "obvious to try" the solution adopted by the inventor. Citing *KSR*, the Federal Circuit has made it clear that a claimed invention may be invalid for obviousness if it was "obvious to try" only if: (1) there were a finite number of options to choose from; (2) the options were all known to a person of ordinary skill; and (3) the results would have been predictable. *Abbott Labs. v. Sandoz, Inc.*, 2008 U.S. App. LEXIS 21880, *24-25, 28 (Fed. Cir. Oct. 21, 2008) ("patentability determinations based on ['obviousness to try'] as the test would not only be contrary to statute but result in a marked deterioration of the entire patent system").

4. Hindsight Is Impermissible

28. 35 U.S.C. §103 requires the Court to determine whether the claimed subject matter "would have been obvious *at the time the invention was made*." The highlighted language requires the Court to turn back the clock to the time when the invention was made and to ask

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[16] *Abbott Labs. v. Sandoz, Inc.*, 2008 U.S. App. LEXIS 21880, *30 (Fed. Cir. Oct. 21, 2008) (distinguishing *KSR* and holding drug nonobvious where there was no "identified, predictable solution"); *Eisai Co. v. Dr. Reddy's Labs.* 520 F.3d 1358, 1364 (Fed. Cir. 2008) (holding drug nonobvious and noting that *KSR's* reference to "identified, predictable solutions" "may present a difficult hurdle" to challengers seeking to invalidate patents in unpredictable arts); *Ortho-McNeil Pharm. Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364-65 (Fed. Cir. 2008) (distinguishing *KSR* and holding drug nonobvious where (a) the person of ordinary skill would have been unlikely to start with the lead compound upon which the drug was based, (b) one from among several unpredictable chemical steps would have to have been chosen to perform on the molecule; and (c) the medical efficacy of the new compound would have been uncertain); *Takeda Chem. Indus. v. Alphapharm Pty.*, 492 F.3d 1350, 1358-61 (Fed. Cir. 2007) (distinguishing *KSR* and holding drug nonobvious where (a) prior art showed "many promising, broad avenues for further research" (b) one reference taught that the lead molecule upon which the drug was based had toxicity problems, and (c) the biological effects of modifying the prior art molecules were unpredictable).

what a person or ordinary skill in the art would have thought *at that time*, guided only by the prior art and the then-accepted wisdom in the field.[17]

5. A Compound Is Not Disclosed By A Prior Art Reference For Purposes Of 35 U.S.C. §§102 Or 103 Merely Because It Is Included Within The Large Genus Of The Reference

29. A prior art reference that discloses a large genus of chemical compounds, *e.g.*, by means of a structural formula allowing certain substituent parts of the molecule to be chosen from lists of preferred atoms, amino acids, or other elements, does not anticipate or render obvious a later claim to a specific individual compound within the scope of that genus.[18]

6. The Examiner's Perceptions Regarding The Prior Art Are Not Binding On The Court

30. A court adjudicating a patent case is *never* bound by the examiner's findings or rulings during prosecution.[19] The only deference a court owes to the PTO is to the PTO's ultimate decision to grant the patent. This deference "takes the form of the presumption of validity that is accorded to issued patents under 35 U.S.C. §282." *Purdue Pharma LP v. Faulding Inc.*, 230 F.3d 1320, 1329 (Fed. Cir. 2000). However, a court owes no deference to individual rulings or

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[17] *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000); *see also KSR* 127 S. Ct. at 1742 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "guard against slipping into the use of hindsight"); *Ortho-McNeil*, 520 F.3d at 1364 (criticizing ANDA filer's use of hindsight).

[18] *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006) (no anticipation of claimed compound where it was "just one of hundreds of compounds included in formula I" of the cited prior art reference); *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) (generic disclosure embracing "millions of compounds" did not render obvious a claim to three specific compounds within the scope of that genus where reference lacked teaching that would have directed a person of ordinary skill to make those three compounds).

[19] *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007) ("Our case law consistently provides that a court is never bound by an examiner's finding in an ex parte patent application proceeding."); *Quad Environ. Techs. Corp. v. Union Sanitary District*, 946 F.2d 870, 876 (Fed. Cir. 1991) ("The courts are the final arbiter of patent validity and, although courts may take cognizance of, and benefit from, the proceedings before the patent examiner, the question is ultimately for the courts to decide, without deference to the ruling of the patent examiner.").

findings by the examiner during the course of ex parte prosecution, particularly on issues that were the subject of testimony at trial.[20]

7. Objective Evidence Of Nonobviousness Must Be Considered

31. Objective evidence of nonobviousness, *e.g.*, evidence that the claimed invention attained commercial success, satisfied a long felt but unsatisfied need, or provided unexpected results,[21] "may often be the most probative and cogent evidence of nonobviousness in the record." *Ortho-McNeil*, 520 F.3d at 1365.

32. The patentee has the burden to show a connection or "nexus" between the objective evidence and the merits of the claimed invention. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). "A *prima facie* case of nexus is generally made out when the patentee shows both that there is commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent." *Id.* at 1392.[22] In pharmaceutical cases, a *prima facie* case of nexus is established by showing that

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[20] *Purdue,* 230 F.3d at 1329 ("The court, however, was not bound by the examiner's finding in the ex parte application proceeding. . . , particularly in light of the fact that the court heard extensive evidence on that issue in an adversary hearing, none of which was before the patent examiner.").

[21] *Ortho-McNeil*, 520 F.3d at 1365 (commercial success, unexpected results, skepticism of experts, and copying); *Eli Lilly,* 471 F.3d at 1380 (long felt need, failure of others, industry acclaim, and unexpected results).

[22] *Demaco*, 851 F.2d at 1394 (*prima facie* case of nexus established where patent covered a special type of paving stone and "it was the patented paving stone that was the thing sold in commerce"); *Winner Int'l Royalty Corp. v. Ching-Rong Wang*, 202 F.3d 1340, 1350 (Fed. Cir. 2000) ("It is presumed that Winner established a nexus between its commercial sales of the [products] and the patented features because they embody the disclosure of the '047 improvement patent.").

the drug is commercially successful and that the patent in suit claims the drug's active ingredient, dosage forms containing it, and/or its indicated uses.[23]

33. Ranbaxy argues that there is no nexus because the medical benefits of Valcyte are not attributable to one limitation of the claimed invention, namely, the requirement that the valganciclovir hydrochloride be *in crystalline form*. But the contribution of the crystalline form limitation would be pertinent only if valganciclovir hydrochloride in *non-crystalline* form had been on sale in the United States or disclosed in a prior art reference before the priority date of the '953 patent application.[24] Valganciclovir hydrochloride was *not* on sale in the United States or disclosed in a prior art reference prior to the filing of the '953 patent application. FF 127, 138, 140, 141. Valganciclovir hydrochloride was a *new molecule*. FF 144.

34. Ranbaxy also argues that the commercial success of Valcyte is due to advertising or other marketing efforts. This is contrary to the record. FF 151. The situation here is analogous to that in other cases where courts concluded that advertising had little effect on the commercial success of the patented drug or medical device.[25]

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[23] *Eli Lilly and Co. v. Zenith Goldline Pharms. Inc.*, 364 F. Supp. 2d 820, 907 (S.D. Ind. 2005) ("In this case, the nexus is presumed because olanzapine embodies the claimed features and is coextensive with the claims of the '382 patent. The '382 patent claims the chemical compound olanzapine, its use to treat schizophrenia . . ., and pharmaceutical dosage forms containing those doses."), *aff'd*, 471 F.3d 1369 (Fed. Cir. 2006).

[24] *Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1345 (Fed. Cir. 2007) (no nexus where products embodying the first three steps of claimed six step method were on sale in the prior art and there was no evidence that the additional steps added by the patent in suit contributed to commercial success); *Syntex (U.S.A.) LLC. v. Apotex, Inc.*, 407 F.3d 1371, 1383 (Fed. Cir. 2005) (no nexus where patent claimed a composition comprising an active ingredient, a preservative, and a stabilizer, where compositions containing the same active ingredient and preservative were in the prior art, and where there was no evidence that commercial success was due to the addition of the stabilizer recited in the claim).

[25] *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1382 (Fed. Cir. 1986) ("the record shows that advertising makes those in the industry – hospitals, doctors, and clinical laboratories – aware of the diagnostic kits but does not make these potential users buy them; the (cont'd)

D. The Written Description Requirement of 35 U.S.C. §112(¶1)

35. To comply with the written description requirement of §112(¶1), the patent specification must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, [the applicant] was in possession of the invention."[26] Compliance with the written description requirement is an issue of fact. *Vas-Cath Inc.*, 935 F.2d at 1562. "A party alleging that a patent is invalid for failure to comply with the written description requirement has the burden of establishing by clear and convincing evidence that the requirement is not met . . . ." *Intirtool, Ltd. v. Texar Corp.*, 369 F.3d 1289, 1294 (Fed. Cir. 2004).

IV. ORDER PURSUANT TO 35 U.S.C. §271(e)(4)(A)

36. Because Roche has established that the commercial sale of Ranbaxy's valganciclovir hydrochloride product will induce infringement of Roche's '953 patent, and Ranbaxy has failed to establish that the patent is invalid, Roche is entitled to entry of an order pursuant to 35 U.S.C. §271(e)(4)(A) directing that the effective approval date of ANDA No. 78-078 shall be not earlier that the date of expiration of Roche's '953 patent, namely, September 29, 2015.[27]

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products have to work, and there is no evidence that that is not the case here or that the success was not due to the merits of the claimed sandwich assays"); *Forest Labs. Inc. v. Ivax Pharms., Inc.*, 438 F. Supp. 2d 479, 495 (D. Del. 2006) (dismissing significance of an "aggressive marketing campaign" in view of testimony that "even good marketing tactics cannot sell a bad drug"), *aff'd in relevant part*, 501 F.3d 1263 (Fed. Cir. 2007).

[26] *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991); *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996) ("If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met.").

[27] Roche reserves the right to submit findings of fact and conclusions of law on the issue of exceptional case under 35 U.S.C. §285 after the Court renders an opinion on the merits in this case.

Respectfully submitted,

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s/ Sheila F. McShane

Bartholomew Verdirame, Esq.
Michael P. Dougherty, Esq.
Tony V. Pezzano, Esq.
Kent Stevens, Esq.
Jeffrey Z. Y. Liao, Esq.
Vinny Lee, Esq.
Christopher Dove, Esq.
CADWALADER, WICKERSHAM & TAFT LLP
1 World Financial Center
New York, New York 10281
Telephone No.: (212) 504-6000
Facsimile No.: (212) 504-6666

David E. De Lorenzi, Esq.
Sheila F. McShane, Esq.
GIBBONS P.C.
One Gateway Center
Newark, New Jersey 07102-5310
Telephone No.: (973) 596-4500
Facsimile No.: (973) 596-0545

Attorneys for Plaintiff Roche Palo Alto LLC